

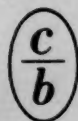
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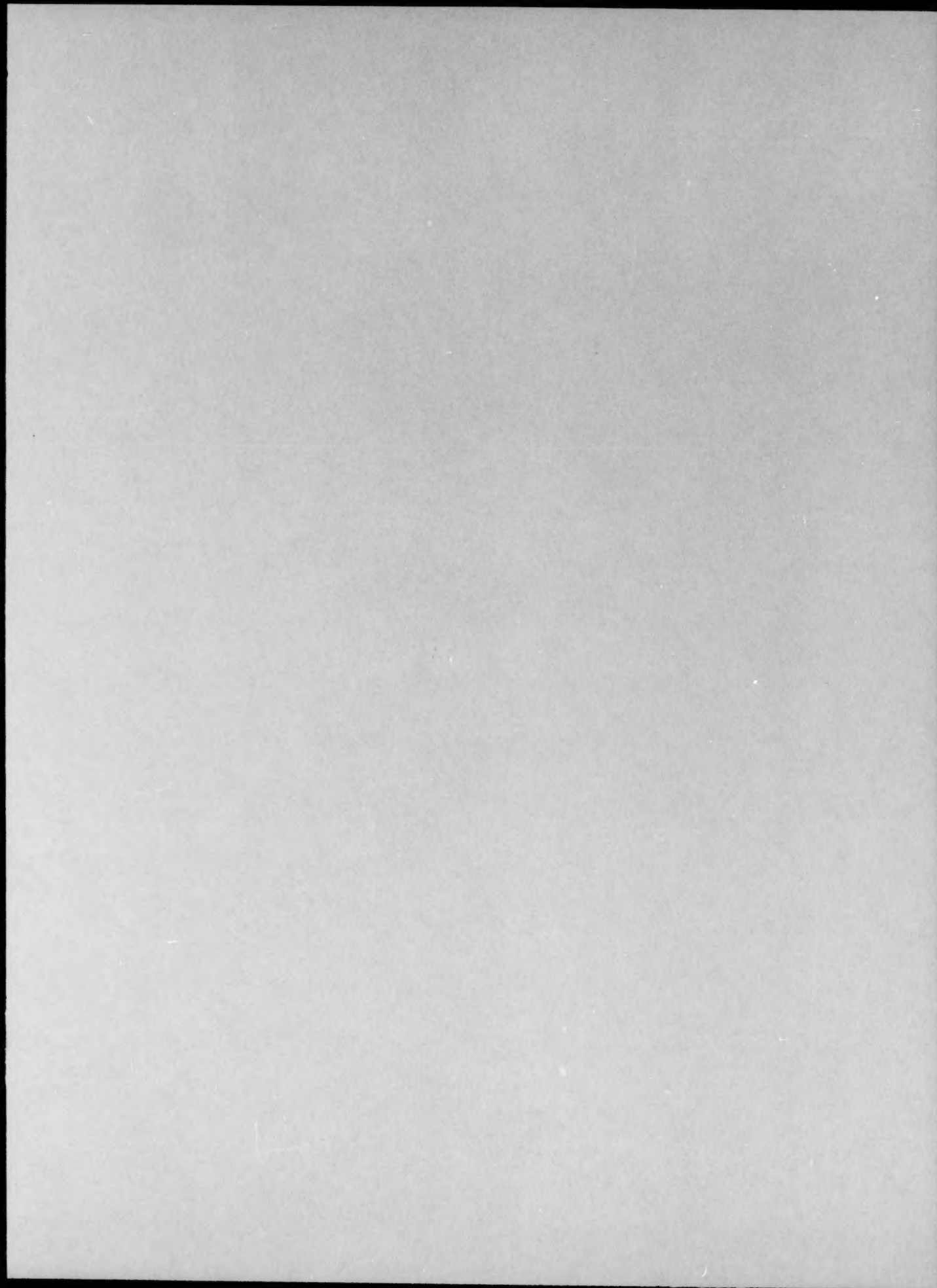
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## COMPLEXING REACTIONS OF ANTIMONY PENTACHLORIDE

### I. CARBOXYLIC ACIDS

M. I. Usanovich, A. K. Nurmakova and T. N. Sumarakova

Institute of Chemical Sciences, Academy of Sciences, Kazakh SSR

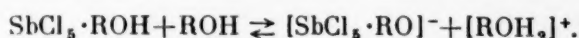
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Complexes of antimony pentachloride with carboxylic acids and alcohols [1], containing one molecule of addend conforming to an  $Sb^{5+}$  coordination number of 6, are described in the literature. To the best of our knowledge, nobody has obtained compounds in which  $SbCl_5$  adds more than one molecule of addend. However, several compounds [2-23] in which the number of molecules of the addends is more than 2 have been obtained for  $SnCl_4(SnBr_4)$ . This apparent increase in the coordination number of tin was explained by the fact [2, 4, 17, 21] that the amphoteric molecules attached to the highly charged central atom are acidified by the mechanism proposed by Meerwein [24] and Grinberg and Faerman [25].

It must be recognized that compounds of the type  $SbCl_5 \cdot ROH$ , where R is an alkyl or an acyl radical, are also complex acids, i.e., capable of splitting off a proton and adding a further molecule of addend in the outer sphere, according to the equation



According to this system, in contrast to compounds  $SbCl_5 \cdot ROH$ , compounds with two molecules of addend must be electrolytes and must be formed with amphoteric substances, for example with carboxylic acids, alcohols and esters.

In the present investigations, an attempt was made to confirm by experiment the existence of  $SbCl_5 \cdot 2ROH$  compounds. For this purpose, the electrical conductivity, viscosity and density of systems formed by  $SbCl_5$  with carboxylic acids were investigated.

### EXPERIMENTAL

Glacial acetic acid was first fractionally frozen; the fraction with an m.p. of 16.65° was redistilled twice. Propionic and butyric acids were dried over copper sulfate and were then repeatedly distilled. In addition, butyric acid was fractionally frozen. Antimony pentachloride ("pure" grade) was redistilled twice under vacuum. All the purified compounds were sealed in ampoules [26].

The compounds had constants which agreed with literature data. For a comparison with the latter, we employed the following procedure. From various literature sources the corresponding graphs of the relation between the given property and temperature were plotted for each compound. Our own data were plotted on these graphs. This method of procedure makes it possible to assess most reliably the agreement of the results of our own measurements with literature data, which at the same time are also critically assessed.

The viscosity and electrical conductivity were measured in the apparatus described in [9]. The density was measured in a pycnometer with a graduated collar. Readings were made by means of an MIR-1 microscope.

For a measurement of the properties a special air-tight cupboard with gloves was used for preparing the mixtures and filling the apparatuses. The atmosphere in this cupboard was kept constantly dry by  $P_2O_5$ .

1. The system  $SbCl_5-CH_3COOH$  was investigated at temperatures of 40, 60 and 80°. The results of the measurements are given in Tables 1 and 2. Figure 1 gives property-composition graphs.

The viscosity isotherms pass through a maximum in the region of 35-40 mole %  $\text{SbCl}_5$ . With an increase in temperature the viscosity maximum becomes flatter and is displaced towards antimony pentachloride. The relation between the constant B (in the equation  $\eta = \frac{B}{Ae^{RT}}$ ) and composition passes through a maximum at 30 mole %  $\text{SbCl}_5$ . As acetic acid is added to antimony pentachloride, the electrical conductivity first increases very slightly and, then, commencing approximately at 50 mole %  $\text{SbCl}_5$ , a marked increase in the conductivity is observed.

TABLE 1. Density and Viscosity of  $\text{CH}_3\text{COOH}-\text{SbCl}_5$  Mixtures

SbCl <sub>5</sub> content		Density (in g/cm <sup>3</sup> )			Viscosity (in centipoises)		
Mole %	Wt. %	40°	60°	80°	40°	60°	80°
0.00	0.00	1.0270	1.0057	0.9825	0.910	0.697	0.554
2.98	13.26	1.1317	1.1090	1.0849	1.56	1.11	0.839
10.00	35.63	1.3468	1.3223	1.2958	4.67	2.76	1.81
12.49	41.55	—	—	—	6.06	3.43	2.20
20.00	55.45	1.5926	1.5676	1.5393	15.5	7.13	3.89
25.03	62.45	—	—	—	—	11.1	5.49
26.80	64.57	—	—	—	26.7	11.4	5.93
29.96	68.06	1.7927	1.7662	1.7377	34.3	14.0	7.26
34.92	72.77	—	—	—	36.3	15.9	8.46
39.64	76.58	1.9506	1.9243	1.8951	36.0	16.9	8.66
42.53	78.66	—	—	—	33.9	16.0	8.59
45.05	80.33	—	—	—	—	15.0	8.11
49.99	83.27	2.0830	2.0514	2.0165	14.6	7.98	4.82
59.59	88.01	—	—	—	5.95	3.83	2.62
70.18	92.14	—	—	—	3.36	2.37	1.79
87.41	97.19	2.2699	2.2327	2.1983	2.04	1.56	1.23
100.00	100.00	2.3063	2.2655	2.2242	1.64	1.26	1.04

TABLE 2. Specific Electrical Conductivity of  $\text{CH}_3\text{COOH}-\text{SbCl}_5$  Mixtures

40°		60°		80°	
Mole %SbCl <sub>5</sub>	$\kappa \cdot 10^3 \text{ ohm}^{-1} \text{ cm}^{-1}$	Mole %SbCl <sub>5</sub>	$\kappa \cdot 10^3 \text{ ohm}^{-1} \text{ cm}^{-1}$	Mole %SbCl <sub>5</sub>	$\kappa \cdot 10^3 \text{ ohm}^{-1} \text{ cm}^{-1}$
0.00	Absent	0.00	Absent	0.00	Absent
6.10	5.02	5.75	5.66	4.51	7.59
7.78	5.45	6.62	6.40	7.20	10.5
9.67	5.53	8.40	7.06	9.81	11.9
11.92	5.34	12.45	7.37	12.94	12.3
13.94	4.98	15.76	7.02	15.87	11.7
17.92	4.22	18.96	6.29	18.95	10.9
21.92	3.46	22.10	5.66	22.03	10.1
24.92	3.01	25.13	5.02	25.01	9.10
27.97	2.63	27.42	4.69	27.36	8.34
30.23	2.40	30.32	4.19	30.47	7.66
33.08	2.20	33.42	3.78	33.14	6.99
35.14	2.09	35.21	3.51	34.99	6.51
37.78	1.93	37.59	3.21	37.65	5.76
39.89	1.78	40.07	2.86	40.22	5.02
45.40	1.23	42.81	2.42	43.12	4.08
50.54	0.439	44.58	2.12	44.58	3.22
60.24	0.0959	48.76	1.18	48.76	1.78
70.96	0.0283	58.61	0.186	58.61	0.228
82.60	0.00248	68.74	0.0445	68.74	0.0343
90.44	$< 1 \cdot 10^{-7}$	81.24	0.00254	81.24	0.00172
100.00	Absent	92.06	$< 1 \cdot 10^{-7}$	92.06	$< 1 \cdot 10^{-7}$
		100.00	Absent	100.00	Absent

The shape of the specific conductivity isotherm reflects the formation of two compounds. The equimolecular compound existing in the crystalline state [1] is not an electrolyte: therefore in the left-hand part of our graph (50-100 mole %  $\text{SbCl}_5$ ) the electrical conductivity is very low compared with the value observed in the right-hand part

of the graph (0-50 mole %  $\text{SbCl}_5$ ); it is due to formation of the compound  $\text{SbCl}_5 \cdot 2\text{CH}_3\text{COOH}$ . From an examination of Fig. 1 it may also be seen that the specific conductivity isotherms have a fairly complex shape, due to the effect of viscosity, which is indicated by the corrected electrical conductivity isotherm ( $\kappa$ ) shown in Fig. 1. The corrected electrical conductivity isotherms have a simple shape: they pass through a maximum at 30 mole %  $\text{SbCl}_5$ , the position of which remains unchanged with a variation in temperature. This maximum is due to formation of the compound  $\text{SbCl}_5 \cdot 2\text{CH}_3\text{COOH}$ , the presence of which leads to the appearance of electrical conductivity in the system. The curve of the temperature coefficient of the conductivity ( $\alpha$ ), which passes through a maximum at about 33 mole %  $\text{SbCl}_5$ , also indicates the existence of a compound of 1 : 2 composition. The system shows a point of inflection, caused by reaction of the components.

TABLE 3. Density and Viscosity of  $\text{C}_2\text{H}_5\text{COOH}-\text{SbCl}_5$  Mixtures

SbCl <sub>5</sub> content		Density (in g/cm <sup>3</sup> )			Viscosity (in centipoises)		
Mole %	Wt. %	40°	60°	80°	40°	60°	80°
0.00	0.00	0.9725	0.9512	0.9304	0.824	0.640	0.521
3.21	11.80	1.0699	1.0479	1.0237	1.41	1.02	0.779
10.18	31.40	1.2463	1.2219	1.1983	3.31	2.15	1.49
15.03	41.66	1.3640	1.3389	1.3127	5.88	3.44	2.21
20.64	51.22	1.4889	1.4624	1.4366	10.3	5.41	3.26
24.92	57.26	1.5753	1.5385	1.5152	13.5	7.01	4.13
29.45	62.76	1.6424	1.6159	1.5895	16.5	8.28	4.82
33.02	66.56	1.7101	1.6836	1.6563	18.8	9.51	5.32
33.99	67.52	—	—	—	18.9	9.60	5.57
36.31	69.71	—	—	—	18.3	9.32	5.37
37.43	70.71	—	—	—	18.6	9.58	5.59
43.31	75.52	—	—	—	17.1	9.06	5.31
43.92	75.97	—	—	—	16.0	8.66	5.16
49.59	79.88	—	1.9233	1.8930	—	5.58	3.74
60.49	86.07	2.0326	2.0176	1.9806	4.52	3.13	2.11
74.25	92.09	—	—	—	2.85	2.01	1.50
87.48	96.58	—	—	—	2.06	1.52	1.18
100.00	100.00	2.3063	2.2655	2.2242	1.64	1.26	1.04

TABLE 4. Specific Conductivity of  $\text{C}_2\text{H}_5\text{COOH}-\text{SnCl}_4$  Mixtures

40°		60°		80°	
mole % $\text{SbCl}_5$	$\kappa \cdot 10^3 \text{ ohm}^{-1} \text{ cm}^{-1}$	mole % $\text{SbCl}_5$	$\kappa \cdot 10^3 \text{ ohm}^{-1} \text{ cm}^{-1}$	mole % $\text{SbCl}_5$	$\kappa \cdot 10^3 \text{ ohm}^{-1} \text{ cm}^{-1}$
0.00	Absent	0.00	Absent	0.00	Absent
3.21	1.39	3.21	1.84	3.21	2.29
5.88	3.01	4.80	2.63	5.71	3.13
11.85	4.18	5.84	3.36	10.37	4.48
15.14	4.32	7.96	4.24	13.40	5.31
20.24	4.22	10.01	4.70	16.99	5.78
24.99	3.67	12.67	5.12	19.57	6.10
28.35	3.24	15.85	5.45	22.45	6.50
30.73	3.09	18.63	5.84	25.63	6.52
32.95	2.69	24.20	5.66	28.53	6.36
35.10	2.47	26.51	5.32	31.06	6.74
37.47	2.33	28.76	5.02	33.31	5.53
39.96	2.04	30.88	4.70	35.61	5.08
43.22	1.62	33.02	4.13	38.31	4.50
45.55	1.02	35.32	3.99	40.87	4.08
49.09	0.45	38.99	3.61	43.43	3.53
59.59	0.0632	42.93	2.77	46.60	2.36
70.18	0.0133	45.77	1.92	50.50	0.645
74.25	$< 1 \cdot 10^{-7}$	47.39	1.38	54.98	0.125
87.48	$< 1 \cdot 10^{-7}$	49.99	0.848	59.44	0.0534
100.00	Absent	59.59	0.111	64.43	0.0218
		74.25	$< 1 \cdot 10^{-7}$	74.25	$< 1 \cdot 10^{-7}$
		87.48	$< 1 \cdot 10^{-7}$	87.48	$< 1 \cdot 10^{-7}$
		100.00	Absent	100.00	Absent



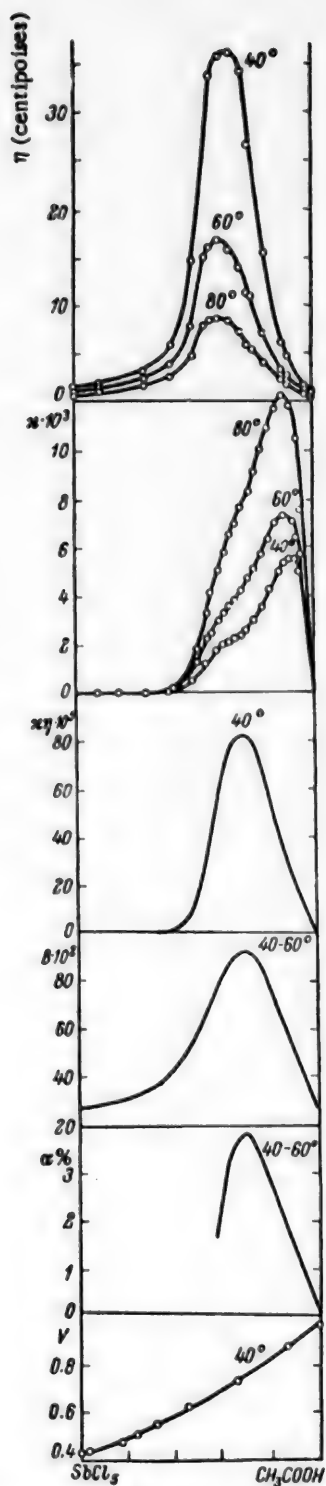


Fig. 1. Property-composition graphs of the system  $\text{SbCl}_5$ - $\text{CH}_3\text{COOH}$ ; composition in mole % for specific volumes in wt. %

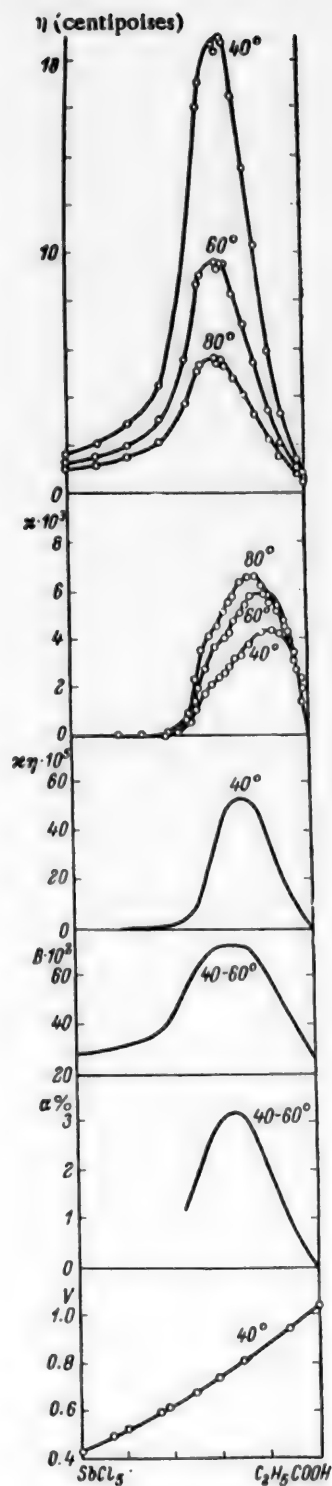


Fig. 2. Property-composition graphs of the systems  $\text{SbCl}_5$ - $\text{C}_2\text{H}_5\text{COOH}$ ; composition in mole % for specific volumes in wt. %.

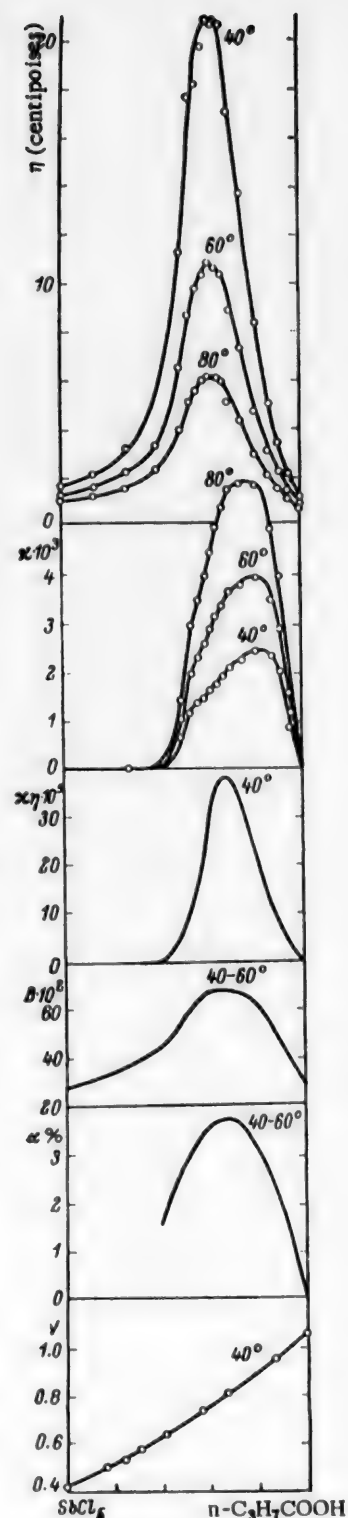


Fig. 3. Property-composition graph of the system  $\text{SbCl}_5$ - $n\text{-C}_3\text{H}_7\text{COOH}$ ; composition in mole % for specific volumes in wt. %

2. The electrical conductivity, viscosity and density of the system  $\text{SbCl}_5\text{-C}_2\text{H}_5\text{COOH}$  were investigated at 40, 60 and 80°. The results of the measurements are given in Tables 3 and 4 and in Fig. 2. The property-composition graphs of this system also indicate reaction of the components.

The viscosity isotherms pass through a maximum, the position of which is displaced towards  $\text{SbCl}_5$  (35-40 mole %  $\text{SbCl}_5$ ) with an increase in temperature. The curve of the relation between the constant B and composition has a maximum at 30 mole %  $\text{SbCl}_5$ . The specific conductivity isotherms have the same shape as in the system  $\text{SbCl}_5\text{-CH}_3\text{COOH}$ . The corrected conductivity isotherms pass through a maximum, the position of which corresponds to 33 mole %  $\text{SbCl}_5$ , i.e., the compound  $\text{SbCl}_5 \cdot 2\text{C}_2\text{H}_5\text{COOH}$ . The formation of a compound 1 : 2 composition is also indicated by the maximum of the curve of the temperature coefficient of the conductivity at 35 mole %  $\text{SbCl}_5$ .

The observed inflection is due to reaction of the components.

3. The system  $\text{SbCl}_5\text{-n-C}_3\text{H}_7\text{COOH}$  was investigated at the same temperatures as the previous ones, i.e., 40, 60 and 80°. The results of the measurements are given in Table 5 and in Fig. 3.

As butyric acid is added to antimony pentachloride the viscosity of the solution increases, passes through a maximum at 35-40 mole %  $\text{SbCl}_5$  and then falls. With a reduction in temperature the viscosity maximum approaches the ordinate of the compound  $\text{SbCl}_5 \cdot 2\text{C}_3\text{H}_7\text{COOH}$ .

The curve of the relation between the constant B and composition, which passes through a maximum at 33 mole %  $\text{SbCl}_5$ , indicates the formation of the compound  $\text{SbCl}_5 \cdot 2\text{C}_3\text{H}_7\text{COOH}$  in the system. The specific conductivity isotherms are similar to those for the systems  $\text{SbCl}_5\text{-CH}_3\text{COOH}$  and  $\text{SbCl}_5\text{-C}_2\text{H}_5\text{COOH}$ . The corrected conductivity isotherms and the curve of the temperature coefficient of conductivity also pass through a maximum at 33 mole %  $\text{SbCl}_5$ . The specific volume isotherms show a constriction which is the result of reaction of the components.

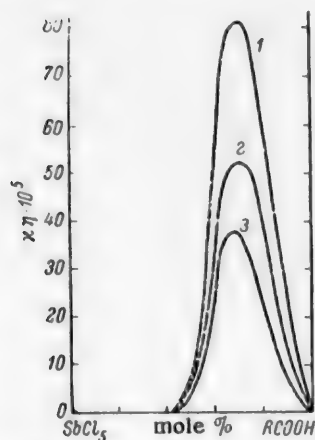


Fig. 4. Comparison of the corrected conductivity isotherms of the systems: 1)  $\text{SbCl}_5\text{-CH}_3\text{COOH}$ ; 2)  $\text{SbCl}_5\text{-C}_2\text{H}_5\text{COOH}$ ; 3)  $\text{SbCl}_5\text{-n-C}_3\text{H}_7\text{COOH}$ .

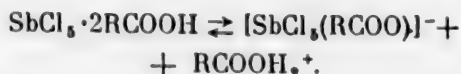
TABLE 5. Density, Viscosity and Specific Conductivity of  $\text{n-C}_3\text{H}_7\text{COOH-SbCl}_5$  Mixtures

SbCl <sub>5</sub> content		Density (in g/cm <sup>3</sup> )			Viscosity (in centipoises)			$\kappa \cdot 10^3 \text{ ohm}^{-1} \text{ cm}^{-1}$		
mole %	wt. %	40°	60°	80°	40°	60°	80°	40°	60°	80°
0.00	0.00	0.9374	0.9195	0.8990	1.17	0.880	0.691	Absent	Absent	Absent
5.01	15.19	1.0497	1.0297	1.0086	2.10	1.45	1.06	0.857	1.18	1.57
9.04	25.22	—	—	—	3.40	2.22	1.52	2.00	2.86	3.96
12.92	33.49	1.2186	1.1971	1.1746	5.04	3.08	2.07	2.31	3.45	4.94
18.50	43.51	1.3305	1.3082	1.2844	8.40	4.71	2.98	2.46	3.93	5.81
24.68	52.65	—	—	—	13.7	7.27	4.31	2.25	3.78	5.87
29.75	58.97	1.5400	1.5165	1.4914	17.1	8.88	5.11	2.05	3.60	5.71
32.96	62.53	—	—	—	20.3	10.4	5.89	1.90	3.36	5.38
34.92	64.55	—	—	—	20.8	10.6	6.01	1.75	3.09	4.96
35.15	64.79	—	—	—	20.7	10.7	6.00	1.76	3.13	4.94
38.06	67.59	—	—	—	20.9	10.8	6.15	1.62	2.85	4.46
39.79	69.17	1.7098	1.6847	1.6586	19.8	10.4	5.96	1.47	2.54	3.96
43.05	71.96	—	—	—	18.2	9.72	5.54	1.36	2.29	3.47
45.96	74.27	—	—	—	15.7	8.71	5.13	1.19	1.98	2.97
49.77	77.08	1.8574	1.8290	1.7999	11.3	6.55	3.88	0.641	1.01	1.40
60.06	83.62	1.9602	1.9298	1.8952	5.13	3.36	2.30	0.0338	0.0465	0.0448
71.88	89.67	—	—	—	3.19	2.22	1.59	0.00782	0.00768	—
86.25	95.51	—	—	—	2.15	1.59	1.21	$< 1 \cdot 10^{-7}$	$< 1 \cdot 10^{-7}$	$1 \cdot 10^{-7}$
100.00	100.00	2.3063	2.2655	2.2242	1.64	1.26	1.04	Absent	Absent	Absent

Therefore the results of measurements of the conductivity, viscosity and density are a definite indication of the existence of the compound  $\text{SbCl}_5 \cdot 2\text{C}_3\text{H}_7\text{COOH}$ .

## DISCUSSION OF THE RESULTS

The investigation of the systems  $\text{SbCl}_5\text{-CH}_3\text{COOH}$ ,  $\text{SbCl}_5\text{-C}_2\text{H}_5\text{COOH}$  and  $\text{SbCl}_5\text{-n-C}_3\text{H}_7\text{COOH}$  by physicochemical analysis method (conductivity, viscosity and density shows that in addition to compounds  $\text{SbCl}_5\cdot\text{RCOOH}^*$ , compounds  $\text{SbCl}_5\cdot 2\text{RCOOH}$  are formed in all these systems. In our opinion, these compounds are electrolytes, dissociating as follows:



The presence of a fairly high conductivity ( $10^{-3} \text{ ohm}^{-1} \text{ cm}^{-1}$ ) in these systems, and the shape of the specific and corrected conductivity isotherms regularly show that the cause of the appearance of conductivity is the formation of the compounds  $\text{SbCl}_5\cdot 2\text{RCOOH}$ .

As one passes from  $\text{CH}_3\text{COOH}$  to  $\text{C}_3\text{H}_7\text{COOH}$  the depth of the secondary acid-base reaction associated with the formation of the compounds  $\text{SbCl}_5\cdot 2\text{RCOOH}$  falls. This is illustrated particularly clearly by a comparison of the values of the corrected conductivity in the investigated systems. From Fig. 4 it may be seen that the corrected conductivity decreases as one passes from  $\text{CH}_3\text{COOH}$  to  $\text{C}_3\text{H}_7\text{COOH}$ . A similar picture is observed in systems formed by  $\text{SnCl}_4$  and  $\text{SnBr}_4$  with carboxylic acids [2-16], esters [17-20] and alcohols [21-23]. This similarity indicates a fundamental analogy in the behavior of tin tetrahalides and antimony pentachloride with respect to oxonium bases (carboxylic acids, esters and alcohols). Like tin halides, antimony chloride forms addition products in which the coordination number  $\text{Me}^{\text{II}}$  is increased to 6. However, addition of a greater number of addends is possible. In this case addition of addends takes place in the outer sphere of the complex; during this process electrolytes are formed, the presence of which leads to the appearance of conductivity in these systems.

Halides of trivalent antimony behave in a different way with respect to oxonium bases. The appearance of conductivity in these systems is due to the formation of products involving  $[\text{SbX}_2(\text{ROH})]^+\text{X}^-$  and  $[\text{SbX}_2(\text{ROH})]^+ [\text{SbX}_4]^-$  [27-34].

## SUMMARY

1. The viscosity, density and conductivity of the systems  $\text{SbCl}_5\text{-CH}_3\text{COOH}$ ,  $\text{SbCl}_5\text{-C}_2\text{H}_5\text{COOH}$  and  $\text{SbCl}_5\text{-n-C}_3\text{H}_7\text{COOH}$  were investigated at 40, 60 and 80°.
2. The existence of complexes of antimony pentachloride of the type  $\text{SbCl}_5\cdot 2\text{RCOOH}$  was established.
3. A system was proposed for the electrolytic dissociation of complexes of this type:



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# PHYSICOCHEMICAL INVESTIGATION OF THE SYSTEM

## ACETIC ACID-PIPERIDINE

A. S. Naumova

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The investigation of acetic acid systems is of both theoretical and practical interest because in a number of cases this acid is used as a solvent and as a medium for carrying out a number of chemical reactions [1].

In [2] we investigated acetic acid mixed with pyridine, which is a fairly strong organic base, by the electrical conductivity method. When acetic acid is mixed with pyridine an acid-base reaction takes place, which is clearly expressed on graphs of the electrical conductivity and other properties. The process of decomposition of the associated acid molecules during dilution with pyridine is not reflected on the composition-property graphs.

The object of the present investigation was to study the behavior of acetic acid when mixed with piperidine, which in aqueous solution is the strongest of known organic bases ( $K_b = 1.6 \cdot 10^{-3}$ ). We investigated the system acetic acid-piperidine by the method of fusibility, electrical conductivity, viscosity and density.

TABLE 1. Crystallization Temperatures of  $C_6H_{11}N-CH_3COOH$  Mixtures

Acid content (in mole %)	Crystallization temperature	Acid content (in mole %)	Crystallization temperature
0.00	-8.60	51.00	101.20
1.14	29.20	55.64	93.60
2.44	44.15	57.98	87.60
2.93	47.80	60.23	79.00
3.46	51.70	65.01	44.60
6.08	65.60	66.84	24.20
11.46	80.20	67.80	15.40
18.57	85.70	89.45	-1.50
26.03	94.48	91.10	4.00
32.45	98.62	92.45	8.20
42.03	101.40	93.60	10.20
49.08	101.60	100.00	16.20

## EXPERIMENTAL

The crystallization temperatures were determined by the visual-polythermic method. The liquid homogeneous phase was investigated at 70 and 90°. The conductivity was measured by the Kohlrausch method in a sealed vessel with platinized platinum electrodes. A tube generator of audio frequency with an amplifier was used as the constant-current source. The viscosity was investigated by means of a sealed Ostwald viscometer. The density was determined in a 2 ml pycnometer.

The acetic acid was purified by repeated fractional freezing. The final freezing was carried out in sealed ampoules, in which it was kept. The m.p. of the purified acid was 16.2°, the b.p. was 117-118° at 757.9 mm H. Piperidine was dried with caustic potash and was then distilled. The fraction with a b.p. of 105.5-106° at 754.3 mm was used for the measurements.

Mixing of the components was accompanied by marked liberation of heat and simultaneously by crystallization. Solutions of acetic acid and piperidine have a tendency to considerable supercooling. Cooling converts mixtures con-

taining 70-88 mole % of the acid to a glycerine-like, noncrystallizable mass. Mixtures with 56-62% of the acid are sublimated. The crystallization curve (Table 1, Fig. 1) passes through a maximum at 50 mole %.

TABLE 2. Density and Viscosity of  $C_8H_{11}N-CH_3COOH$  Mixtures

Acid content (in mole %)	Density		Viscosity (poises)	
	70°	90°	7 °	90°
0.00	0.8182	0.7981	0.0063	0.0047
5.35	0.8340	0.8126	0.0074	0.0053
9.30	0.8501	0.8290	0.0086	0.0061
21.17	0.8999	0.8760	0.0185	0.0119
23.82	0.9196	0.8920	0.0235	0.0144
29.94	0.9489	0.9228	0.0478	0.0250
30.98	0.9520	0.9301	0.0583	0.0316
33.72	0.9665	0.9460	0.1151	0.0475
38.08	0.9850	0.9640	0.1492	0.0686
42.66	0.9981	0.9609	0.1761	0.0839
45.70	1.0010	0.9882	0.1853	0.0884
48.99	1.0102	0.9953	0.1909	0.0940
51.74	1.0140	1.0000	0.1919	0.0945
54.84	1.0180	1.0041	0.1859	0.0938
61.72	1.0251	1.0103	0.1660	0.0883
67.17	1.0284	1.0140	0.1186	0.0650
69.50	1.0309	1.0161	0.1115	0.0617
70.49	1.0291	1.0130	0.1047	0.0581
74.59	1.0322	1.0181	0.0702	0.0403
81.89	1.0309	1.0152	0.0394	0.0253
91.81	1.0240	1.007	0.0169	0.0117
100.00	0.9995	0.9758	0.00609	0.0048

TABLE 3. Specific Conductivity of  $C_8H_{11}N-CH_3COOH$  Mixtures

Acid content (in mole %)	Specific conductivity $\kappa \cdot 10^4 \text{ ohm}^{-1} \text{ cm}^{-1}$		Acid content (in mole %)	Specific conductivity $\kappa \cdot 10^4 \text{ ohm}^{-1} \text{ cm}^{-1}$	
	70°	90°		70°	90°
9.58	0.146	0.109	59.25	91.83	138.20
14.71	2.79	2.47	62.99	109.30	158.50
18.37	8.54	8.85	66.94	120.70	177.10
21.17	15.93	18.27	73.02	139.30	197.50
24.85	24.78	30.34	78.33	159.70	229.90
30.98	41.81	56.39	79.71	165.90	236.80
33.72	46.06	63.86	84.50	185.10	253.60
41.06	55.64	83.63	87.93	177.8	241.50
46.58	58.82	89.22	91.69	141.00	193.50
51.02	64.61	103.80	95.46	70.87	94.44
54.15	77.95	115.70	100.00	0.0083	0.014
56.75	83.38	125.05	—	—	—

The viscosity isotherms (Table 2, Fig. 1) have a clearly expressed maximum, corresponding to 50 mole %. At 70° the maximum is more acute. With a reduction in temperature the viscosity increases considerably. The relation between density and composition (Table 2, Fig. 1) is expressed by curves which are convex with respect to the composition axis, indicating a considerable positive deviation from the additive value, i.e., the formation of solutions of acetic acid with piperidine is accompanied by contraction.

The conductivity isotherms (Table 3, Fig. 1) show a maximum in the region of 85 mole % of acid and a break, corresponding to 50 mole %

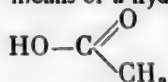


## DISCUSSION OF THE RESULTS

The marked liberation of heat, crystallization and the reduction of the volume during mixing of piperidine with acetic acid indicate that the components react. The presence of a maximum on the crystallization curve (at 50 mole %)

indicates the formation of a fairly stable compound  $C_5H_{11}N \cdot CH_3COOH$  in the system. We isolated this compound and determined its nitrogen content by microanalysis\* (by Dumas' method). The analytical data confirm the indicated composition of the compound.

The crystallization temperature of this compound was determined ( $101.75^\circ$ ), but since its liquid phase has a tendency to considerable supercooling, it is possible that accuracy of the measurements was affected. The congruent crystallization temperature of the compound ( $101.75^\circ$ ) is far higher than the value for the pure components (melting point of acetic acid  $+16.2^\circ$ , and for piperidine  $-8.6^\circ$ ). As is shown by the crystallization curve, the compound exists in a fairly wide concentration range. The compound forms white plates, insoluble in ether, difficultly soluble in benzene and readily soluble in alcohol and water; they are very hygroscopic. The liquid phase becomes golden-yellow when heated. Assuming that the acid is attached to piperidine by means of a hydrogen bond, the structure  $C_5H_{11}N \dots$



may be attributed to this compound.

As might be expected, the compound formed by the reaction of piperidine and acetic acid is stabler than the corresponding pyridine compound. Thus, the compound of acetic acid and piperidine melts at a temperature far higher than the melting point of the pure components, whereas the melting point of its compound with pyridine is lower than the melting points of the components [3, 4]. Mixtures of acetic acid and piperidine have a high electrical conductivity [1] and viscosity [5]. The system acetic acid-piperidine also

differs from the system acetic acid-pyridine by the fact that in a specific concentration range, the solutions form a glycerine-like noncrystallizable mass when cooled. The ability to undergo supercooling is evidently explained by the presence in the liquid phase of molecules—dimers of acetic acid, piperidine and the compound formed in the system—of different size and structure [6]. In all probability the concentration of the first and last of these is high, because the dielectric permeability of piperidine (5.8) is less than that for pyridine (12.4) [7].

## SUMMARY

1. The crystallization curve of the system acetic acid-piperidine was obtained. The presence of a congruently melting compound ( $C_5H_{11}N \cdot CH_3COOH$ ) was established. The compound was isolated, its crystallization temperature and melting point were determined.
2. The conductivity, viscosity and density of the liquid phase were investigated at 70 and  $90^\circ$ . Graphs of these properties confirm the existence of this compound in the system.
3. A probable structure of the compound formed by acetic acid and piperidine is given.

\* The analysis of the nitrogen content was carried out by Z. M. Murav'eva.

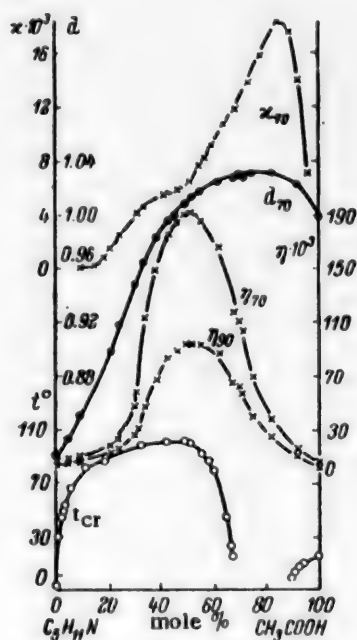


Fig. 1. Collated graph of properties of the system acetic acid-piperidine:  $t_{cr}$ ) crystallization temperature;  $\kappa$ ) specific conductivity (in  $ohm^{-1} cm^{-1}$ ),  $\eta$ ) viscosity (in poises,  $d$ ) density.



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# THE MAGNETIC SUSCEPTIBILITY OF BINARY LIQUID SYSTEMS

O. E. Kashireninov, O. A. Osipov, M. A. Panina  
and V. N. Marchenko

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Investigations of the magnetic susceptibility of binary liquid systems were carried out for the first time by A. Smith and D. Smith [1]. They showed that the susceptibility of mixtures is a linear function of the magnetic susceptibilities of the components, even in such systems as water-acetone and ethyl alcohol-water. Subsequent investigations by N. A. Trifonov [2, 3] and others [4-10] established that in the majority of cases the magnetic susceptibility of binary liquid systems does not obey the Videmann additivity law. However, in some cases these deviations from additivity are so slight that they may not be due to physicochemical changes in the system, but to experimental errors. For this reason, there are a number of contradictory views in the literature with regard to data on the magnetic susceptibility of binary liquid systems [11-13].

The Videmann additivity law for the magnetic susceptibility of a mixture

$$\chi = \sum \chi_i P_i \quad (i = 1, 2, 3, \dots, n), \quad (1)$$

where  $\chi_i$  and  $P_i$  are the susceptibility and the weight of the  $i$ -component respectively, is correct only for normal or near-normal systems. This equation is inapplicable, not only to solid solutions containing paramagnetic ions, but also to systems the components of which change their molecular state as a result of mixing. Therefore, deviations of the experimental values of the magnetic susceptibility from linearity may be employed for assessing the physicochemical processes taking place during the mixing of components.

Chemical reaction between the components must distort to a certain degree the shape of the electron atmosphere of the molecules, which in turn leads to an increase of the polarization paramagnetism in the diamagnetic molecules

TABLE 1. System  $C_6H_6-CCl_4$   
 $\mu_1^* = 0, \mu_2^* = 0$

(in wt. %)	$-\chi_p \cdot 10^{-6}$	$\Delta\chi_p \cdot 10^{-6}$
100.0	0.702	
60.4	0.596	0.0
33.7	0.526	-0.001
14.5	0.473	+0.001
0.0	0.435	

\* $\mu$  - Value of the dipole moment  
in Debyes.

of the components of the system and to deviation of the magnetic susceptibilities of mixtures from the additive values [14, 15]. Alteration of the electron density as a result of chemical reaction between the components must change the integral values of the polarities of the molecules taking part in the reaction. There must therefore be a direct relation between the magnetic susceptibility of binary liquid systems and the polarity of their components. In point of fact, Ranganadhan [7, 8] showed that deviation of the magnetic susceptibility from additivity is greatest in systems consisting of polar components. He explained this phenomenon by molecular deformation as a result of the reaction of the dipoles of the components. However, Buchner [6] considers that this effect cannot have a great influence on the magnetic properties.

To determine the effect of the polarity of the components on the susceptibility of mixtures, we investigated the magnetic susceptibility of a number of binary liquid systems. The results of these investigations are given below.

# EXPERIMENTAL

The substances employed were carefully purified by the method we have previously described [16-18]. The magnetic susceptibilities were measured by the Gouy method [19, 20] in the fields of about 5000-8000 oersteds. The pole shoes of the magnets were shaped like truncated cones, the diameter of the planar part being about 7 cm, and therefore the magnetic field in the gap was completely uniform. The poles had a very low residual intensity of magnetization. To ensure a constant field strength and eliminate convection currents, which may influence substantially the accuracy of weighing, the magnets were equipped with cooling devices. The gap between the pole shoes and the outer wall of the ampoule containing the substances was not less than 2.5-3 mm.

The apparent variations in weight of the ampoule with the investigated substance were determined by means of a microanalytical balance, the calibration of the weights of the latter being checked by the authors. The same solution was weighed not less than 3 times. It must be noted that we introduced a correction for the variation of the magnetic susceptibility of the ampoule wall in the magnetic field.

TABLE 2. System  $C_6H_5CHO-CH_3COC_2H_5$   
 $\mu_1 = 2.77$  D,  $\mu_2 = 2.75$  D

(in wt. %)	$-x_g \cdot 10^{-6}$	$\Delta x_g \cdot 10^{-6}$
100.0	0.569	
81.5	0.583	+0.001
69.2	0.596	-0.003
59.4	0.601	-0.001
49.5	0.611	-0.003
30.2	0.623	0.0
0.0	0.646	

TABLE 3. System  $C_5H_5N-C_9H_7N$   
 $\mu_1 = 2.20$  D,  $\mu_2 = 2.18$  D

(in wt. %)	$-x_g \cdot 10^{-6}$	$\Delta x_g \cdot 10^{-6}$
100.0	0.616	
65.4	0.632	+0.002
48.0	0.644	-0.001
33.7	0.649	+0.002
28.2	0.653	+0.001
17.3	0.660	-0.001
0.0	0.668	

TABLE 4. System  $iso-CH_3COOC_5H_{11}-CH_3(CH_2)_4COOCH_3$   $\mu_1 = 1.80$  D,  
 $\mu_2 = 1.76$  D

(in wt. %)	$-x_g \cdot 10^{-6}$	$\Delta x_g \cdot 10^{-6}$
100.0	0.693	
80.0	0.690	+0.001
60.0	0.691	-0.001
50.0	0.689	+0.001
40.0	0.689	0.00
20.0	0.688	+0.001
0.0	0.686	

The specific magnetic susceptibility was calculated by means of the equation

$$\chi_2 = \chi_1 \cdot \frac{\Delta w_2}{\Delta w_1} \cdot \frac{m_1}{m_2} \quad (2)$$

where  $\chi_2$  and  $\chi_1$  are the specific susceptibilities of the investigated substance and standard respectively,  $\Delta w_2$  and  $\Delta w_1$  are the variations in weight of the investigated substance and standard in the magnetic field, and  $m_2$  and  $m_1$  are their respective masses.

We employed carefully purified benzene, saturated with air, as the standard. Its specific magnetic susceptibility given in a published tabulation [20] is  $-0.702 \cdot 10^{-6}$ . We also determined the susceptibility of benzene by means of the equation

$$\chi_1 = \frac{2 \cdot l \cdot \Delta w_1}{H_{\max}^2 \cdot m \cdot 1.019} \quad (3)$$

where  $l$  is the height of the benzene column, in centimeters (in our experiments it was 15 cm),  $\Delta w_1$  is the variation in weight of benzene in the magnetic field,  $H_{\max}$  is the magnetic field strength in the inter-polar gap, in oersteds.

For benzene we obtained a specific magnetic susceptibility of  $-0.703 \cdot 10^{-6}$ . This figure is the mean of 5-6 measurements which differed from one another by not more than two units in the third sign of decimals, i.e., the error did not exceed 0.5%.

## RESULTS OF THE INVESTIGATION AND THEIR DISCUSSION

Tables 1-10 give the results of an investigation of the specific magnetic susceptibility of the systems benzene-carbon tetrachloride, methyl ethyl ketone-benzaldehyde, pyridine-quinoline, isoamyl acetate-methyl caproate, acetone-n-butyl alcohol, diethyl ether-chloroform, aniline-acetic acid, stannic chloride-acetic acid. The final columns of the Tables give the deviations of the experimental values of the specific magnetic susceptibility from the additive values. As may be seen from the data of Table 1, the system formed from benzene and carbon tetrachloride, the molecules of which do not have a dipole moment, has a linear specific magnetic susceptibility isotherm (the concentration being expressed in wt. %).

Here the deviations from additivity do not exceed  $\pm 0.2\%$ . Our data agree satisfactorily with Seely's [21], which also showed that the specific magnetic susceptibility of mixtures consisting of two non-polar liquids is a linear function of concentration.

TABLE 5. System  $(\text{CH}_3)_2\text{CO}-n\text{-C}_4\text{H}_9\text{OH}$   
 $\mu_1 = 2.72 \text{ D}$ ,  $\mu_2 = 1.68 \text{ D}$

(in wt. %)	$-x_g \cdot 10^{-3}$	$\Delta x_g \cdot 10^{-3}$
100.0	0.580	
75.8	0.626	-0.007
54.0	0.666	-0.012
43.9	0.687	-0.016
34.3	0.699	-0.013
16.4	0.720	-0.009
0.0	0.741	

TABLE 6. System  $(\text{C}_2\text{H}_5)_2\text{O}-\text{CHCl}_3$   
 $\mu_1 = 1.15 \text{ D}$ ,  $\mu_2 = 1.15 \text{ D}$

(in wt. %)	$-x_g \cdot 10^{-3}$	$\Delta x_g \cdot 10^{-3}$
100.0	0.765	
71.3	0.663	+0.023
48.2	0.583	+0.041
38.3	0.551	+0.046
29.3	0.526	+0.046
13.4	0.505	+0.024
0.0	0.492	

TABLE 7. System  $\text{C}_6\text{H}_5\text{N}_2-\text{CH}_3\text{COOH}$   
 $\mu_1 = 1.51 \text{ D}$ ,  $\mu_2 = 1.60 \text{ D}$

(in wt. %)	$-x_g \cdot 10^{-3}$	$\Delta x_g \cdot 10^{-3}$
100.0	0.690	
86.1	0.632	+0.035
78.3	0.605	+0.049
75.6	0.593	+0.058
69.9	0.581	+0.060
60.8	0.565	+0.062
43.7	0.535	+0.065
39.9	0.534	+0.058
27.9	0.530	+0.043
0.0	0.527	

TABLE 8. System  $\text{SnCl}_4-\text{C}_2\text{H}_5\text{COOC}_4\text{H}_9$   
 $\mu_1 = 0$ ,  $\mu_2 = 1.77 \text{ D}$

(in wt. %)	$-x_g \cdot 10^{-3}$	$\Delta x_g \cdot 10^{-3}$
100.0	0.443	
89.7	0.447	+0.015
76.5	0.453	+0.034
68.4	0.465	+0.037
59.1	0.474	+0.046
52.0	0.473	+0.039
35.1	0.543	+0.021
0.0	0.630	

TABLE 9. System  $\text{SnCl}_4-\text{iso-C}_6\text{H}_5\text{COOC}_6\text{H}_{11}$   
 $\mu_1 = 0$ ,  $\mu_2 = 2.20 \text{ D}$

(in wt. %)	$-x_g \cdot 10^{-3}$	$\Delta x_g \cdot 10^{-3}$
100.0	0.443	
84.4	0.461	+0.014
67.0	0.487	+0.016
57.5	0.503	+0.018
47.5	0.520	+0.020
40.4	0.536	+0.016
25.3	0.565	+0.014
0.0	0.625	

TABLE 10. System  $\text{SnCl}_4-\text{CH}_3\text{COOH}$   
 $\mu_1 = 0$ ,  $\mu_2 = 0.83 \text{ D}$

(in wt. %)	$-x_g \cdot 10^{-3}$	$\Delta x_g \cdot 10^{-3}$
100.0	0.443	
94.6	0.344	+0.100
86.7	0.250	+0.205
81.3	0.204	+0.257
68.4	0.161	+0.317
52.0	0.231	+0.268
0.0	0.564	

The investigation of the behavior in electric and magnetic fields of systems consisting of two polar components, the molecules of which have similar dipole moment values is of considerable interest. In one of our previous communications [17] we showed by way of a number of examples that the dielectric permeability isotherms of systems with similar values of the dipole moments of the components obey the additivity law in the whole range of concentrations. We observed the same pattern of such systems in a magnetic field. From the data of Tables 2-4 it is clearly evident that the specific magnetic susceptibility isotherms of the systems benzaldehyde-methyl ethyl ketone, pyridine-quinoline and isoamyl acetate-methyl caproate have a linear shape.

In these systems deviations of susceptibility from additivity do not exceed  $\pm 0.5\%$ , which is within the limits of experimental error. The results of these investigations show that both the magnetic susceptibilities of systems consisting of two nonpolar components and the susceptibilities of systems formed by two polar non-reacting components with similar values of the dipole moments obey the additivity law. Our data confirm the results of an investigation by Trew and Watkins [22] of the specific magnetic susceptibility of the system isopropyl alcohol-n-butyl alcohol. Such behavior of the systems shows that the intermolecular forces are practically unchanged during mixing of the components. In mixtures consisting of non-reacting associated liquids these forces depend on the values of the inner local fields created by the polar molecules. Therefore, as a first approximation it may be assumed that the dipole moment is a criterion of these forces. Thus, systems formed from two components with equal values of the dipole moments must be similar in behavior to normal systems. Judging by the dielectric permeability and magnetic susceptibility isotherms and certain other properties [23], they are indeed similar to them.

Table 5 gives the values of the specific magnetic susceptibility of the system acetone-n-butyl alcohol.

The dipole moments of the components in this system differ considerably from each other; therefore its behavior in a magnetic field must be different from that of the systems examined above. As a matter of fact, the deviations of the experimental values of the specific magnetic susceptibility from additivity have a negative sign, i.e., the mixtures are more diamagnetic than the pure components. This may probably be explained by decomposition of the associated molecules of the components, principally of alcohol, for which, as a result of chain association, polarization paramagnetism is greater than for the monomer. Finally, it may be noted that for the system diethyl ether-chloroform, aniline-acetic acid, stannic chloride-butyl propionate, stannic chloride-isoamyl benzoate, stannic chloride-acetic acid (Tables 6-10), deviations of the specific magnetic susceptibility isotherms from linearity have positive values.

It must be noted that the maximum deviations of susceptibility occur in the region of concentrations close to the composition of the molecular compounds (discovered by other physicochemical methods of investigation [24-26]) formed in the system as a result of a hydrogen or donor-acceptor bond; therefore magnetic susceptibility may find extensive application in physicochemical analysis.

For systems in which chemical reaction takes place, the equality or difference of the dipole moments of the components does not play an important role, because the behavior is mainly determined by the character of the reaction of the components.

#### SUMMARY

1. The magnetic susceptibility of the following binary systems was investigated: benzene-carbon tetrachloride, benzaldehyde-methyl ethyl ketone, pyridine-quinoline, isoamyl acetate-methyl caproate, acetone-n-butyl alcohol, chloroform-diethyl ether, aniline-acetic acid, stannic chloride-butyl propionate, stannic chloride-isoamyl benzoate and stannic chloride-acetic acid.
2. It is shown that the magnetic susceptibility isotherms of systems consisting of components with similar values of the dipole moments are linear in the whole concentration range.
3. It was established that in the case of chemical reaction between the components with formation of a hydrogen or donor-acceptor bond, the deviations of the magnetic susceptibility isotherms from additivity have positive values and the maximum deviations correspond to the composition of the compound formed.

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## INVESTIGATIONS IN THE FIELD OF THE CHEMISTRY OF ALLENE COMPOUNDS

### IV. THE DIRECTION OF BROMINATION AND HYDROBROMINATION OF UNSYMMETRICAL ALLENE HYDROCARBONS\*

A. V. Fedorova and A. A. Petrov

Lensovet Leningrad Technological Institute

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The direction of reactions involving addition of electrophilic reagents to unsymmetrical allene hydrocarbons has not been closely investigated. Addition of bromine to methylallene gave 2,3-dibromobutene-1, which even at room temperature is readily converted, evidently to 1,2-dibromobutene-2 [1]. According to literature data, bromination of ethyl- and propylallenes takes place similarly, with formation of 2,3-dibromopentene-1 [1] and 2, 3-dibromohexene-1 [2]. However, bromination of unsymmetrical dimethylallene gave only 1, 2-dibromo-3-methylbutene-2 [3].

Literature data on the direction of addition of hydrogen halides to unsymmetrical allenes are no less scant and contradictory. Hydrochlorination of propylallene takes place with formation of 2-chlorohexene-2 [4], hydrobromination of ethylallene gives 2-bromopentene-1, possibly with an admixture of 2-bromopentene-2 [5]. Hydrobromination of dimethyl- and diethylallenes gives 3-bromo-3-methylpentene-1 [6] and 1-bromo-3-ethylpentene-2 [7].

Whereas in the case of bromination both possible addition products are linked by an allyl rearrangement, and the absence of a specific regularity may be explained by slight differences in the conditions under which different authors obtained and treated the addition products, in the case of hydrobromination only two of the four addition products can be converted into each other as a result of allyl rearrangement. Here, literature data, if correct, indicate fundamental differences in the order of addition of hydrogen bromide in relation to the structure of the allene hydrocarbon.

With the aim of establishing the general laws in the direction of addition of bromine and hydrogen bromide to unsymmetrical allene hydrocarbons we repeatedly investigated the bromination and hydrobromination of propylallene and unsymmetrical dimethylallene, for which (according to literature data) different directions in these two reactions are observed.

According to [2], the bromination product of propylallene is primarily 2, 3-dibromohexene-1. With ozonization it gave a considerable amount of formaldehyde. The infrared spectrum of the dibromide was almost identical with the spectrum of 2, 3-dibromohexene-1, obtained by dehydrobromination of 1, 2, 3-tribromohexane [2] (Fig. 1, curves 1 and 2). The spectra of the substances obtained by both methods show only one frequency of stretching vibrations of the double bond ( $1620\text{ cm}^{-1}$ ), which may only be attributed to the  $\text{CH}_2=\text{C} <$  group not to the  $-\text{CH}=\text{C} <$  group, and only one frequency of deformation CH-vibrations ( $900\text{ cm}^{-1}$ ), which may also be attributed to the  $\text{CH}_2=\text{C} <$  group. The spectrum of the dibromide obtained by the latter method shows stronger absorption at  $960$  and  $1220\text{ cm}^{-1}$ , evidently due to admixtures.

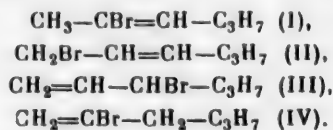
Contrary to [3], bromination of dimethylallene gave primarily 2, 3-dibromo-3-methylbutene-1. With ozonization it gave a considerable amount of formaldehyde. In the infrared spectrum of this dibromide a strong valence frequency of the end double bond was observed at  $1620\text{ cm}^{-1}$ , together with a weak frequency of  $1645\text{ cm}^{-1}$ , characteristic of isomeric 1,2-dibromo-3-methylbutene-2 (Fig. 1, curves 3 and 4). We prepared the later by dehydrobromination of 1,2,3-tribromo-3-methylbutane. It did not give formaldehyde when ozonized.

\* For communication III, see *ZhOKh*, 30, 2949 (1960).



Therefore it was established that electrophilic bromination of unsymmetrical alkyl- and dialkylallenes always takes place at the more substituted double bond, with formation of labile 2,3-dibromoalkene-1 capable of isomerization to 1,2-dibromoalkene-2. The previously reported order of addition of bromine to unsymmetrical dimethylallene does not correspond to the facts. Evidently, allyl rearrangement took place during treatment of the dibromide.

It might be expected that addition of hydrogen bromide to propylallene would give four addition products:



The substances actually obtained were practically devoid of (allyl) bromine atoms and formulas (II) and (III) are therefore inapplicable to them. This conclusion was confirmed by analysis of the infrared spectra of the hydrobromides. Only weak absorption was observed in the 900-1000  $\text{cm}^{-1}$  region.\*

The choice between formulas (I) and (IV) for the main part of the hydrobromide was made on the basis of a comparison of the infrared spectrum of the addition product with the spectra of the known bromides (I) and (IV).

Bromide (I) was obtained by bromination and dehydrobromination of hexene-2 [8] and bromide (IV) was obtained by the same methods from hexene-1 [9].\*\* In both cases the substances obtained contained small amounts of the other possible isomers with halogen at the double bond, but this did impede our investigation.

As might be expected, isomeric bromides (I) and (IV) differ markedly as regards the position of the band of the double-bond stretching vibrations: substance (I) corresponds to the 1628  $\text{cm}^{-1}$  strong band, and bromide (IV) to the 1662  $\text{cm}^{-1}$  band. Furthermore, a strong 885  $\text{cm}^{-1}$  band is characteristic

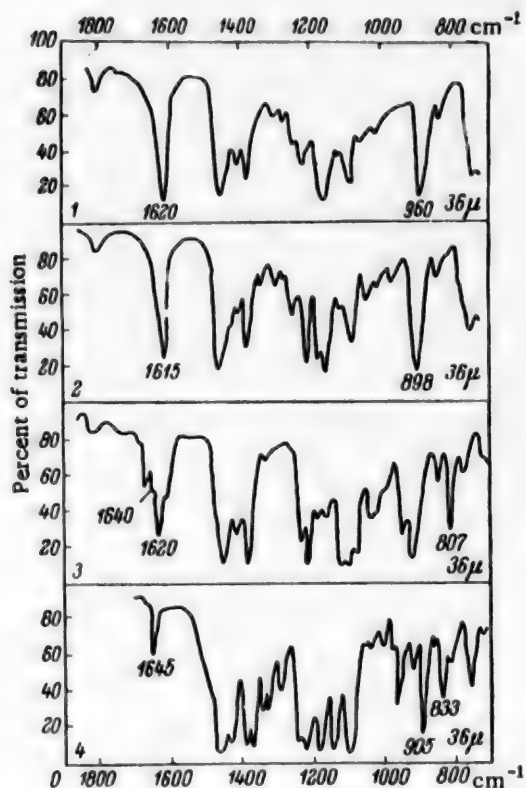
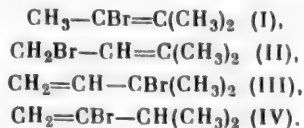


Fig. 1. Infrared transmission spectra: 1) addition products of bromine and propylallene; 2) 2,3-dibromohexene-1; 3) addition products of bromine and dimethylallene; 4) 1,2-dibromo-3-methylbutene-2.

of dibromide (IV). The ratio of the strengths of these bands in the spectrum of the addition product of hydrogen bromide and propylallene indicated that it contained at least 90% of bromide (I) (Fig. 2).

Therefore, hydrogen bromide is not added to propylallene at the same double bond at which bromine is added.

It might be expected that addition of hydrogen bromide to dimethylallene would also give four addition products:



\* As is known, compounds containing a vinyl group or a  $-\text{CH}=\text{CH}-$  grouping are absorbed in this region.

\*\* When attempts were made to obtain bromide (IV) by the action of HBr on hexene-1, primarily 1-bromohexene-1, with characteristic strong bands of 921 and 947  $\text{cm}^{-1}$  in the infrared spectrum was obtained. In the presence of hydroquinone a mixture of two bromides is also obtained, but with a higher content of 2-bromohexene-1 (characteristic band 885  $\text{cm}^{-1}$ ).

The hydrobromine actually obtained had a lachrymatory odor and contained 86% of mobile (allyl) bromine. Formulas (I) and (IV) are therefore excluded for the main part of the substance. The hydrobromide did not differ from the ordinary hydrobromide of isoprene (II) as regards the infrared spectrum. Bromides (I) and (IV) obtained by cross

synthesis had different constants and characteristic frequencies in the infrared spectra (Fig. 2). In this way we confirmed literature data on the direction of addition of hydrogen bromide to dimethylallene. Here, as in the case of bromination, the more substituted double bond is evidently more active. However, as a result of allyl regrouping, hydrobromide (II), corresponding formally to the addition of hydrogen bromide at the less substituted double bond is obtained (contrary to Markownikov's Rule).

Therefore as a result of this investigation it was established that the order of addition of hydrogen bromide depends on the character of substitution in an allene system. Further investigations are required for an explanation of the laws discovered.

#### EXPERIMENTAL

Propyl- and unsymmetrical dimethylallenes were prepared by reduction of the corresponding acetylene chlorides by zinc in butyl alcohol (by the Ginzburg method) [10]. The boiling points and refractive indices of the hydrocarbons obtained were practically the same as those given in the literature. Judging by the infrared spectrum, dimethylallene did not contain an appreciable admixture of isopropylacetylene (Fig. 3, curve 1). Weak absorption at  $3300\text{ cm}^{-1}$  was observed in the infrared spectrum of propylallene, indicating the presence of an admixture of butylacetylene (Fig. 3, curve 2).

**Bromination of propylallene.** To a solution of 5 g of hydrocarbon in 50 ml of anhydrous chloroform was added dropwise with cooling ( $-10$ – $-15^\circ$ ) and stirring 8 g of bromine and 30 ml of chloroform. 8.2 g of bromides was added, the major part of which distilled under vacuum over  $1^\circ$  range.

**2,3-Dibromohexene-1.** B.p.  $60$ – $61^\circ$  (5 mm),  $d_4^{20}$  1.5920,  $n_D^{20}$  1.5125, MR 45.63; calculated 45.96.

0.4 g of the substance was ozonized in 25 ml of ethyl chloride. The ozonides were decomposed with a 20% potassium iodide solution. The iodine was back-titrated with hyposulfite. A sample of the solution obtained was then heated with an acidified saturated solution of  $\beta$ -naphthol. The precipitate of dinaphtholmethane was separated, dried and weighed.

Calculated with respect to all the initial solution, 0.222 g of dinaphtholmethane was obtained, corresponding to 48% of the theoretical amount of formaldehyde (calculated on 2,3-dibromohexene-1) [11].

We obtained 2,3-dibromohexene-1 as follows:

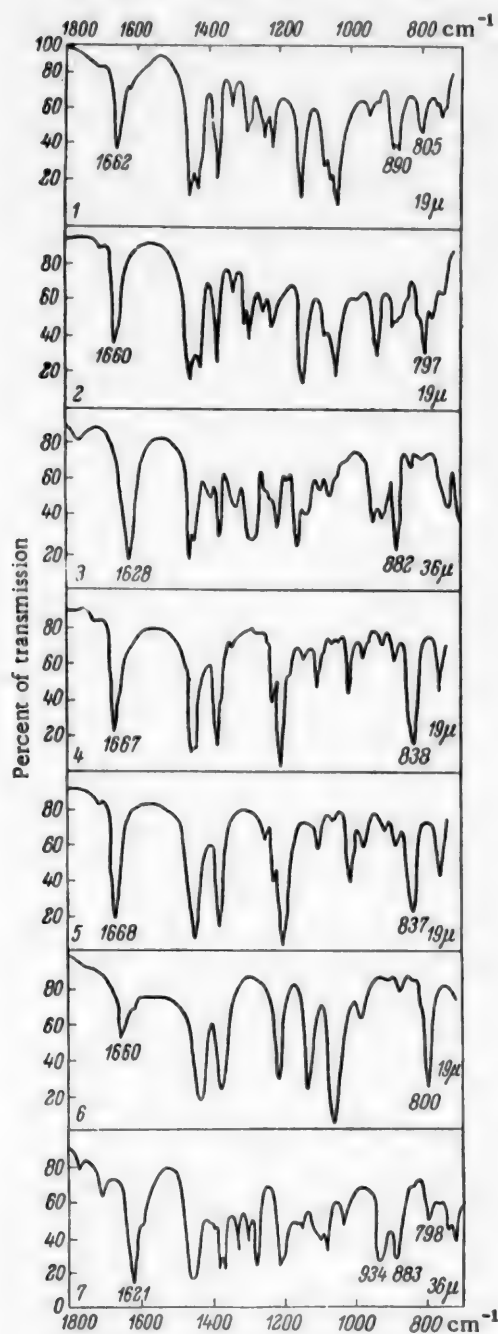
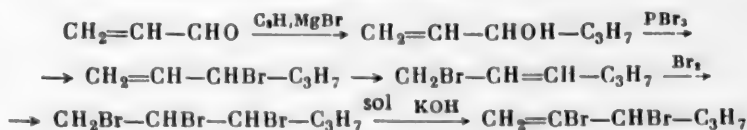


Fig. 2. Infrared transmission spectra: 1) addition products of HBr and propylallene; 2) 2-bromohexene-2; 3) 2-bromohexene-1; 4) addition products of HBr and dimethylallene; 5) 1-bromo-3-methylbutene-2; 6) 2-bromo-3-methylbutene-2; 7) 2-bromo-2-methylbutene-1.

B. p. 62-64° (5 mm)  $d_4^{20}$  1.5930,  $n_D^{20}$  1.5142, MR 45.74; calculated 45.97.

**Bromination of unsymmetrical dimethylallene.** A solution of 2.5 ml of bromine and 12 ml of chloroform was added dropwise with cooling (ice + salt) and efficient stirring to a solution of 5 g of hydrocarbon in 50 ml of chloroform. The hydrocarbon was then distilled together with part of the chloroform and half the initial amount of bromine was added to it under the same conditions. Distillation and bromination of the distillate were then repeated. The reaction mixture and the residues from the first distillations were distilled under vacuum. We obtained 7 g of dibromides, the major part of which distilled over a 1° range.

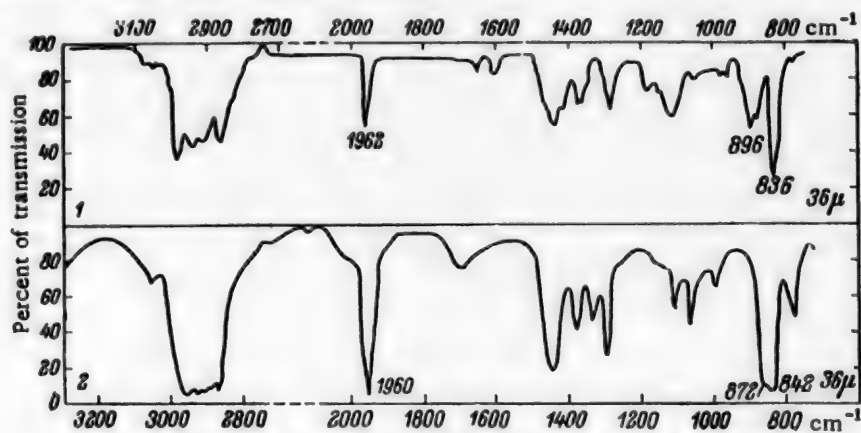
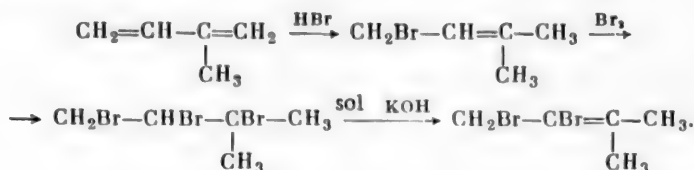


Fig. 3. Infrared transmission spectra: 1) dimethylallene; 2) propylallene.

2,3-Dibromo-3-methylbutene-1 with an admixture of 1, 2-dibromo-3-methylbutene-2. B.P. 65-66° (10 mm),  $d_4^{20}$  1.6520,  $n_D^{20}$  1.5212, MR 41.95; calculated 41.99.

Ozonolysis of the substance under the above-indicated conditions gave 42% of the theoretical yield of formaldehyde (calculated as dinaphtholmethane).

1,2-Dibromo-3-methylbutene-2 was obtained as follows:



Dehydrohalogenation of 1,2,3-tribromo-3-methylbutane was carried out by distillation under vacuum over solid alkali.

B.P. 66-67° (10 mm),  $d_4^{20}$  1.6810,  $n_D^{20}$  1.5126, MR 41.99; calculated 41.99.

Formaldehyde was not formed by ozonolysis of the substance under the above-indicated conditions.

**Hydrobromination of propylallene.** A solution of 5 g of the hydrocarbon in 5 g of HBr in dry ether was shaken for 5 days. The reaction mixture was then washed with water, dried over  $\text{CaCl}_2$  and distilled. The yield was 3.5 g (distillation residue 0.7 g).

Hydrobromide (primarily 2-bromohexene-2): b.p. 58-59.5° (50 mm),  $d_4^{20}$  1.2120,  $n_D^{20}$  1.4662.

Found % Br 49.87, 50.00  $\text{C}_6\text{H}_{11}\text{Br}$ . Calculated % Br 49.09.

Mobile bromine was not found: bromine was not removed when the substance was allowed to stand for 1 hour with 10% KOH.

2-Bromohexene-2 was obtained by distillation of 2,3-dibromohexene over solid KOH [8]. The b.p. was 58-59° (50 mm),  $d_4^{20}$  1.2050,  $n_D^{20}$  1.4652.

2-Bromohexene-1 was obtained in a similar way from 1,2-dibromohexane [9]. The b.p. was 63-64° (50 mm),  $d_4^{20}$  1.2080,  $n_D^{20}$  1.4609.

Hydrobromination of dimethylallene. A solution of 5 g of dimethylallene and 6 g of HBr in 15 ml of absolute ether was shaken for 5 days. Reaction was 80% (according to the reduction in the HBr content). Subsequent procedure was the same as in the previous experiment. The yield was 4 g (residue 1 g).

Hydromide (principally 1-bromo-3-methylbutene-2); b.p. 55-57° (50 mm),  $d_4^{20}$  1.2840,  $n_D^{20}$  1.4912.

Found % Br 53.65, 53.71.  $C_5H_8Br$ . Calculated % 53.66.

The amount of mobile bromine was 86%. 1-Bromo-3-methylbutene-2 was obtained by hydrobromination of isoprene [12]. The b.p. was 55-56° (50 mm),  $d_4^{20}$  1.2720,  $n_D^{20}$  1.4930.

2-Bromo-3-methylbutene-2 was obtained by the action of alcoholic KOH on trimethylethylene dibromide [13]. The b.p. was 42.5-43° (50 mm),  $d_4^{20}$  1.2870,  $n_D^{20}$  1.4722.

2-Bromo-3-methylbutene-1 was obtained by distillation of isopropylethylene dibromide [14]. The b.p. was 32-34° (50 mm),  $d_4^{20}$  1.2410,  $n_D^{20}$  1.4545.

The infrared spectra were determined in an IKS-14 spectrophotometer (thickness of the layer 36 $\mu$ ) or in an IKS-15 spectrophotometer (thickness of the layer 19 $\mu$ ).

#### SUMMARY

1. The direction of addition of bromine and hydrogen bromide to propyl- and dimethylallenes was investigated.
2. It was established that bromine is added directly to both hydrocarbons preferentially at the most substituted double bond.
3. It was shown that during hydrobromination of propylallene, addition of HBr takes place at the less substituted bond, while during hydrobromination of dimethylallene it takes place at the more substituted double bond.

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## MASS SPECTRA AND THE STRUCTURE OF ORGANIC COMPOUNDS

### VI. MASS SPECTRA OF ALKENYL VINYLACETYLENES

A. A. Polyakova and A. A. Petrov

All-Union Scientific-Research Institute for Processing of Petroleum  
and Gas Leningrad Technological Institute

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The investigation of the relation between the structure of hydrocarbons and the distribution of the strengths of the ion currents in their mass spectra has recently made it possible to discover a number of interesting laws which bring us within sight of a solution of the main problem, i.e., the determination of molecular structure from the data of mass-spectrometric investigations.

One of the obstacles to a clear solution of this problem is the presence in the mass spectra of organic compounds of ions whose formation cannot be explained by simple bond rupture. In some cases it is accompanied by migration of hydrogen, while in others it is assumed that a more fundamental skeletal rearrangement takes place. The intensity of the ions originating from the rearrangements increases with an increase in the number of multiple bonds in the molecule.

For saturated and ethylenic hydrocarbons the disintegration of the excited molecular ion takes place primarily with formation of  $C_3H_X^+$  ions. In a number of dienoid and enoid hydrocarbons the most stable ion of this group is  $C_3H_3^+$ , which possibly has the structure of the cyclopropenylum ion.

In the case of 1,3-dienoid, allene and acetylenic hydrocarbons (of normal or moderately branched structure), an additional maximum for  $C_5H_X^+$  ions is shown on the mass distribution curves of the ions [1-3]. The most intense of these, the  $C_5H_6^+$  ion may also be considered to have the cyclic structure of a cyclopentadienylum cation [4].

On the distribution curve for enoid hydrocarbons the second maximum is displaced towards higher masses -  $C_6H_X^+$  [1-3].

Dissociative ionization of benzene homologs takes place with the formation of the stable ion  $C_7H_7^+$ , to which the cyclic structure of the tropylium ion may be fairly safely attributed [5]. Tropyliene (cycloheptatriene-1,3,5) and spirocycloheptadiene-1,3 also form this ion as a result of disintegration in the mass spectrometer [5, 6].

The discovery of these laws makes it possible already at this stage to pose the question of the preferential paths of formation of one or other fragmental ion during the disintegration of an excited molecular ion. The solution of this problem is assisted by an investigation of the mass spectra of hydrocarbons labeled with  $C^{13}$  and  $H^2$  [5, 7] and also by the detection of metastable ions which are specific "indicators" of a certain stage of the disintegration process [8].

To obtain further information on the relation between the character of mass spectra and molecular structure we investigated the mass spectra of a number of dienoid hydrocarbons.\*

The investigation of addition reactions of these hydrocarbons made it possible to determine certain laws associated with structure. Thus, for example it was established that electrophilic addition of hypobromites to propenyl- and isopropenylacetylenes takes place in different ways: in the first case at the unsubstituted double bond, and in the second case at the substituted one [9]. However, in both cases lithium-alkyls are added at the unsubstituted double bond [10, 11].

\* The hydrocarbons were prepared by Yu. I. Porfir'eva.

# Mass Spectra of Dienoid Hydrocarbons

Ion masses	Propenylvinyl- acetylene, C <sub>7</sub> H <sub>8</sub>	Allylvinyl- acetylene, C <sub>7</sub> H <sub>8</sub>	Isopropenylvinyl- acetylene, C <sub>7</sub> H <sub>8</sub>	Crotylvinyl- acetylene, C <sub>8</sub> H <sub>10</sub>	Allylisopropenyl- acetylene, C <sub>8</sub> H <sub>10</sub>	5-Methylocta- diene-1,6-ine-3, C <sub>8</sub> H <sub>12</sub>	Prehnylvinyl- acetylene, C <sub>8</sub> H <sub>12</sub>
1	2	3	4	5	6	7	8
15	—	1.2	4.4	—	—	—	—
26	3.1	4.8	4.7	5.6	—	—	—
27	8.9	11.5	12.9	21.0	—	23.0	20.0
29	—	—	0.4	2.8	—	59.0	50.0
37	1.7	3.7	5.4	2.8	2.4	—	4.9
38	8.6	7.2	10.4	8.8	9.0	7.7	25.0
39	41.4	27.8	37.0	55.8	52.0	87.6	100
41	2.5	2.6	3.7	12.7	13.6	35.9	35.0
42	0.5	—	0.4	0.8	—	—	6.2
43	—	1.2	1.6	0.8	—	—	2.6
49	1.5	1.2	3.3	1.6	0.8	—	1.8
50	9.5	6.0	26.6	13.9	15.3	22.6	47.9
51	7.6	9.9	56.2	23.9	31.0	56.0	39.6
52	3.1	4.3	14.0	12.4	9.7	21.8	40.7
53	2.6	3.9	10.4	8.0	—	28.6	22.7
54	—	—	—	5.6	—	—	2.6
55	—	—	—	—	—	—	11.4
61	2.3	3.4	6.6	1.4	3.1	—	3.1
62	5.1	7.8	12.5	7.6	9.7	5.5	17.2
63	11.7	17.3	26.2	20.7	24.3	24.0	54.6
64	3.3	5.7	14.1	6.0	6.3	3.0	10.2
65	37.5	27.3	33.1	42.6	38.3	27.0	53.7
66	1.0	5.5	8.7	7.6	—	3.4	4.5
67	—	—	—	—	—	3.4	8.9
73	0.54	0.5	2.5	0.8	0.2	—	—
74	2.2	1.5	12.0	5.2	3.4	5.1	12.5
75	1.1	0.8	7.0	3.9	1.5	5.5	14.3
76	0.5	0.6	3.3	2.8	1.0	3.0	9.4
77	3.3	2.2	16.2	32.9	42.2	94.8	70.7
78	0.2	0.2	1.2	34.4	15.9	26.5	23.4
79	—	—	—	3.0	18.0	83.7	66.8
80	—	—	—	—	0.8	3.4	—
85	0.9	0.8	—	—	—	—	0.3
86	1.4	1.2	2.0	—	0.8	—	0.7
87	0.8	0.8	1.6	—	0.6	—	1.2
88	—	0.2	—	—	—	—	0.2
89	3.8	3.3	4.6	3.2	1.7	1.5	—
90	—	3.8	4.1	2.4	0.1	—	—
91	100	100	100	100	100	44.0	40.2
92	28.6	36.8	89.5	8.0	5.7	12.0	10.4
93	—	—	—	—	—	3.0	7.0
103	—	—	—	10.1	—	26.0	21.4
104	—	—	—	4.4	—	6.4	3.9
105	—	—	—	21.9	17.1	100	82.4
106	—	—	—	43.4	35.3	5.1	1.9
119	—	—	—	—	—	5.8	1.9
120	—	—	—	—	—	47.4	46.1
K* mol.	0.405	0.278	0.682	0.199	0.474	0.313	0.340
K <sub>max</sub>	1.47	0.754	0.770	0.444	1.34	0.664	0.736
Complete ioniza- tion	1.45	0.790	1.47	0.805	1.53	1.58	2.40

\* K-sensitivity with respect to benzene.

It would be interesting to compare these and other chemical properties with various physical properties of di-  
enoid hydrocarbons, particularly their behavior to electronic impact.



Dienoid hydrocarbons of the molecular formula ( $C_nH_{2n-6}$ ) are isomeric with aromatic hydrocarbons - homologs of benzene. Therefore it would be desirable to establish analogies in the directions of their disintegration by electronic impact with corresponding data for aromatic hydrocarbons.

The Table gives the mass spectra (obtained in a modified MS-1 apparatus) of three  $C_7H_8$  hydrocarbons isomeric with toluene, with different carbon skeleton structures and different positions of the multiple bonds, two  $C_8H_{10}$  hydrocarbons isomeric with ethylbenzene, and two  $C_9H_{12}$  hydrocarbons.

The mass spectra of the three isomeric alkenyl vinylacetylenes  $C_7H_8$  are characterized by an analogous distribution of the ion current strengths. The maximum are  $C_7H_7^+$  (91) ions; considerable amounts of ions with masses of 65 and 63 are also formed. The probability of disintegration of molecular ions,  $W_z^*$ , depends on the structure of the alkenyl radical (Fig. 1). The molecular ions of isopropenylvinylacetylene ( $W_z = 16.4\%$ ) is the most stable with respect to electronic impact. The strength of the  $C_7H_7^+$  ions in this case is 18.3%, the total amount of fragmental ions is 81.7%.

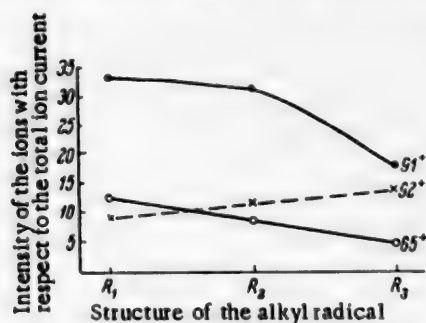
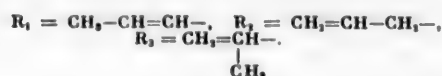


Fig. 1. The effect of the structure of the alkenyl radical on the intensity of formation of molecular and fragmental ions:



The molecular ion of allylvinylacetylene ( $W_z = 11.8\%$ , the amount of  $C_7H_7^+$  ions = 32.1%) undergoes somewhat more fundamental conversion.

Of the three isomers investigated, propenylvinylacetylene undergoes the most extensive disintegration:  $W_z = 9.7\%$ , and the amount of  $C_7H_7^+$  and  $C_6H_5^+$  ions is 1.9 and 2.4 times more than in the case of isopropenylvinylacetylene.

The formation of considerably greater amounts of  $C_4H_X^+$  ions than in the case of the other isomers is also characteristic of isopropenylvinylacetylene.

Crotylvinylacetylene (IV)\* and the isomeric allylisopropenylacetylene (V) dissociate mainly in a similar way to  $C_7H_8$  hydrocarbons. The maximum in their spectrum is the  $C_7H_7^+$  ion, and the stability of the molecular ion is 9.8 and 7.7% respectively.

As one passes to alkenyl vinylacetylenes  $C_9H_{12}$  the distribution of the intensities in the mass spectra changes somewhat; however, it remains similar to isomers characterized by a different position of the methyl groups. In the mass spectra of these hydrocarbons the most intense ion is  $C_9H_9^+$  (105), and the stability of the molecular ion is 6.7 and 7.4%.

The specific directions of dissociative ionization are illustrated by the distribution curves of the ion intensities with respect to the number of hydrocarbons atoms (Fig. 2). For comparison, data for toluene, ethylbenzene and xylenes are given in the same Figure.

All the distribution curves are characterized by the two maxima, usual for highly unsaturated compounds, corresponding to  $C_9H_7^+$  or  $C_4H_9^+$  and  $C_8H_X^+$  or  $C_6H_X^+$  ions. In addition, a third maximum, corresponding to  $C_7H_X^+$  ions (for  $C_7H_8$  and  $C_8H_{10}$  hydrocarbons) or  $C_6H_X^+$  ions (for  $C_9H_{12}$  hydrocarbons), is also observed for dienoid hydrocarbons. This maximum is also characteristic of aromatic hydrocarbons.

From the above examination of the mass spectra and distribution curves of the ion intensities it follows that when dienoid hydrocarbons react with electrons, ions with masses of 105 ( $C_9H_9^+$ ), 91 ( $C_7H_7^+$ ) and also fragmental ions  $C_3H_3^+$  (39),  $C_6H_3^+$  (63) and  $C_6H_5^+$  (65) are preferentially formed. These data allow us to propose the following general system of disintegration of the molecular ions of dienoid hydrocarbons as a result of electronic impact.

\* The probability of disintegration,  $W_z$ , is determined by the ratio between the intensity of the molecular ion and the total ion current:  $W_z = \frac{I_{mol}}{I_{mol} + \Sigma I_{frag}}$ .

\*\* The hydrocarbon contained up to 20% of the isomeric 5-methylheptadiene-1,6-ine-3.



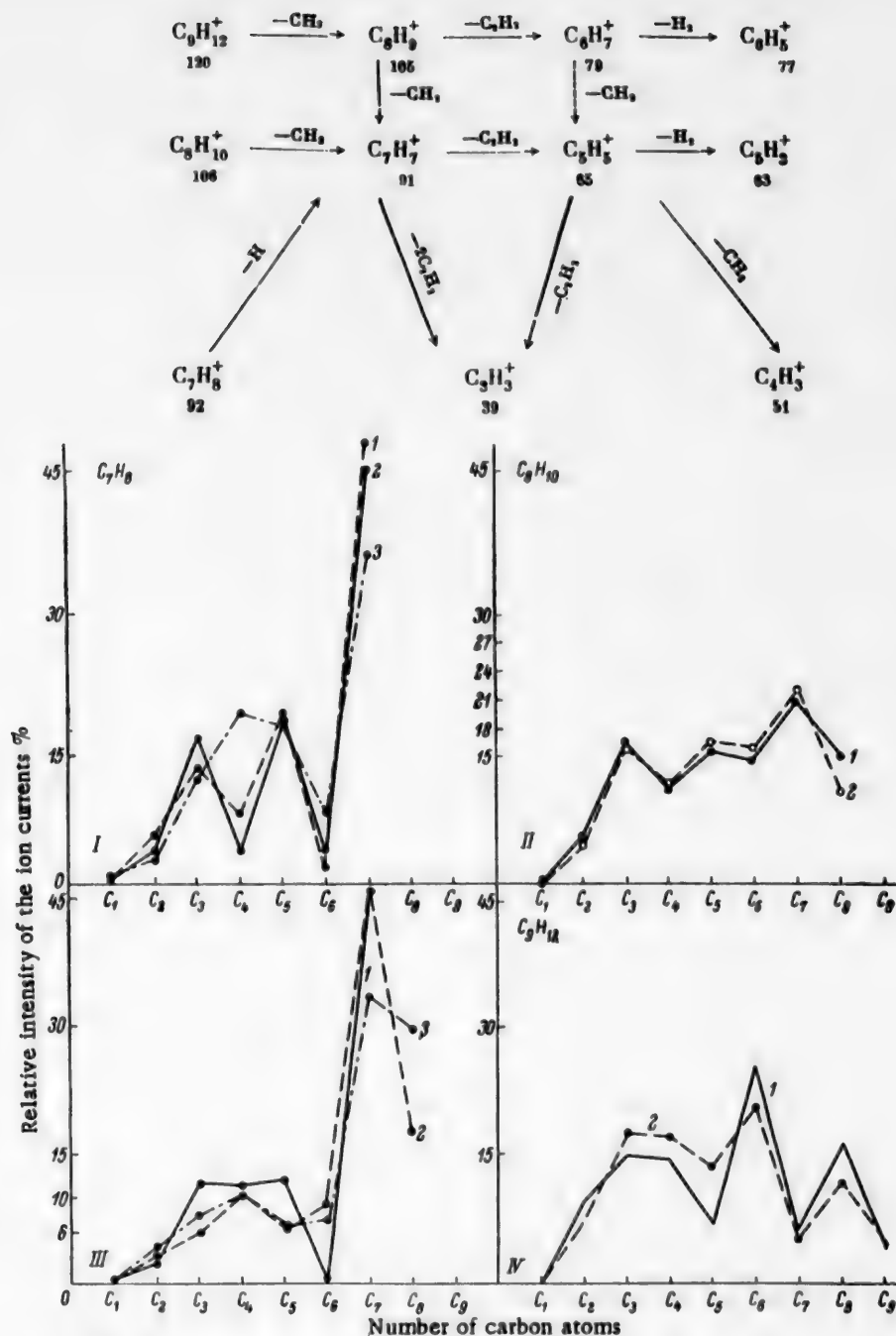


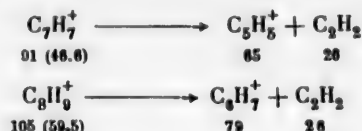
Fig. 2. Distribution of intensities in the mass spectra of dienoid hydrocarbons: I-1) allylvinylacetylene; 2) propenylvinylacetylene; 3) isopropenylvinylacetylene; II-1) crotylvinylacetylene; 2) allylisopropenylacetylene; III-1) toluene; 2) ethylbenzene; 3) xylenes (mean of three isomers); IV-1) 5-methyloctadiene-1,6-diene-3 2) prehnilylvinylacetylene.

The central place in this system is occupied by the  $C_7H_7^+$  ion, which possibly has the structure of the tropylium ion. In the case of  $C_7H_8$  hydrocarbons it is formed as a result of removal of hydrogen from the molecular ion, and in the case of  $C_9H_{10}$  hydrocarbons - as a result of removal of a methyl radical.

During the disintegration of the  $C_7H_7^+$  ion with removal of acetylene, two other ions  $C_5H_5^+$  and  $C_3H_3^+$ , of characteristic mass spectra are formed. Since all seven carbon atoms of the tropylium ion are equivalent, removal of acetylene may be effected in several ways, which increases considerably the probability of this process.

This system of disintegration of the  $C_7H_7^+$  ion for  $C_7H_8$  and  $C_8H_{10}$  hydrocarbons is confirmed by the presence of a metastable ion with a mass of 46.6 (intensity 0.5%) in their spectra.

As one passes to the higher members of the series, the general system of dissociative ionization is somewhat complicated, but the basic stages of the process are described by the same reactions. In the case of  $C_9H_{12}$  hydrocarbons, the first stage of disintegration is removal of a methyl group, with formation of the most prominent ion in the spectrum,  $C_8H_9^+$  (105). The position of the methyl group in the chain does not have an important influence on its intensity. The formation of other fragmental ions evidently takes place by removal of methylene groups, acetylene or hydrogen from the  $C_8H_9^+$  ion. The sequence of the proposed reactions is confirmed by the presence of metastable ions with masses of 46.6 and 59.5 in the mass spectra.



The presence of analogies in the formation of fragmental ions in the mass spectra of  $C_7$ - $C_9$  dienoid hydrocarbons makes it possible to assume that during the process of dissociation of the  $C_8H_9^+$  ion the carbon skeleton is rearranged, with formation of a seven-membered ring.

Assuming cyclic structures for the principal ions in the gaseous phase makes it possible to explain the absence of essential differences in the mass spectra of isomeric dienoid hydrocarbons - alkylbenzenes, cycloheptatriene, vinyl-alkyl acetylenes, etc.

For a closer examination of our theories on the mechanism of dissociative ionization of highly unsaturated compounds, we will subsequently carry out an investigation of the spectral response of  $C_5H_5^+$ ,  $C_6H_5^+$  and  $C_7H_7^+$  ions and examine their corresponding energy characteristics.

#### SUMMARY

1. The mass spectra of the following seven dienoid hydrocarbons were investigated: heptadiene-1,5-ine-3, heptadiene-1,6-ine-3, 2-methylhexadiene-1,5-ine-3, octadiene-1,6-ine-3, 2-methylheptadiene-1,6-ine-3, 5-methyloctadiene-1,6-ine-3, 7-methyloctadiene-1,6-ine-3.
2. The distribution of the ion intensities in the mass spectra was established and the sensitivities and total ionizations with respect to benzene were determined.
3. A general scheme for the disintegration of molecular ions via a stage of formation of cyclic ions is proposed.

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# INVESTIGATIONS IN THE FIELD OF CONJUGATED SYSTEMS

## CXLIV. DIPOLE MOMENTS, STRUCTURE, AND REACTIVITY OF SOME

### ENYNE HYDROCARBONS AND SILICOHYDROCARBONS\*

A. A. Petrov, K. S. Mingaleva, M. D. Stadnichuk,  
and I. A. Maretina

Lensovet Leningrad Technological Institute

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The monotypically constructed enyne hydrocarbons and silicohydrocarbons differ considerably from one another with respect to the direction of additions to the conjugated system. Thus, for example, in the catalytic hydrogenation of enyne hydrocarbons, hydrogen adds to the acetylene bond, while in the case of the silicohydrocarbons it adds predominantly to the ethylene bond [1]. On bromination, the tendency to 1,4-addition observed is greater with the silicohydrocarbons than with the hydrocarbons [2]. Free radicals add to the hydrocarbons in the 1,4-positions and to the silicohydrocarbons at the ethylene bond [3].

TABLE 1. Dipole Moments of Enyne Hydrocarbons and Silicohydrocarbons

Silicohydrocarbon	Dipole moment (D)	Hydrocarbon	Dipole moment (D)
$(\text{CH}_3)_3\text{Si}-\text{C}\equiv\text{C}-\text{CH}=\text{CH}_2$	0.44	$(\text{CH}_3)_3\text{C}-\text{C}\equiv\text{C}-\text{CH}=\text{CH}_2$	0.57
$(\text{CH}_3)_3\text{Si}-\text{C}\equiv\text{C}-\text{CH}=\text{CH}-\text{CH}_3$	0.57	—	—
$(\text{CH}_3)_3\text{Si}-\text{C}\equiv\text{C}-\underset{\text{CH}_3}{\text{C}}=\text{CH}_2$	0.39	$(\text{CH}_3)_3\text{C}-\text{C}\equiv\text{C}-\underset{\text{CH}_3}{\text{C}}=\text{CH}_2$	0.68
$(\text{CH}_3)_3\text{Si}-\text{C}\equiv\text{C}-\underset{\text{CH}_2}{\underset{\text{CH}_2}{\text{C}}}=\text{CH}$	0.89	—	—
$(\text{C}_6\text{H}_5)_3\text{Si}-\text{C}\equiv\text{C}-\underset{\text{CH}_2}{\underset{\text{CH}_2}{\text{C}}}=\text{CH}_2$	0.56	$(\text{C}_6\text{H}_5)_3\text{C}-\text{C}\equiv\text{C}-\text{CH}=\text{CH}_2$	0.85

These and other differences in the reactivity of the hydrocarbons and silicohydrocarbons may be due to steric hindrances caused by the trialkylsilyl group or to a specific displacement of the electron cloud of the conjugated system under the influence of the silicon atom, which has free positions in the d-shell.

In order to elucidate the nature of the differences in the reactivity of enyne hydrocarbons and silicon hydrocarbons, it was of interest to compare those physical properties of these substances that are connected with their structure.

In the present communication, the dipole moments of enyne hydrocarbons and silicohydrocarbons containing trimethylsilyl or tertiary butyl radical, respectively, attached to the triple bonds are compared.

It has been shown earlier that the introduction of methyl radicals into the molecule of vinylacetylene in the 1 (from the triple bond side) or 3 position reduces the dipole moment in comparison with that for unsubstituted vinyl-

\* Enyne compounds LVIII.

TABLE 2. Initial Data for the Determination of the Dipole Moments of Enyne Hydrocarbons and Silicohydrocarbons

Substance	B.p. (pressure in mm)	$d_4^{20}$	$n_D^{20}$	$M R_D$	$t_0$	$\alpha$	$n_D$	$\beta$	$P_{\infty}$
$(CH_3)_3C-C\equiv C-CH=CH_2$ $(CH_3)_3C-C\equiv C-C=CH_2$	47° (100) 60.5-61 (100)	0.7451 0.7519	1.4430 1.4422	38.48 43.03	2.2835 2.2834	0.090 0.202	1.1368 1.1368	0.206 0.188	45.33 53.08
$(C_6H_5)_3C-C\equiv C-CH=CH_2$ $(CH_3)_3Si-C\equiv C-CH=CH_2$ $(CH_3)_3Si-C\equiv C-CH=CH-CH_3$ $(CH_3)_3Si-C\equiv C-C=CH_2$	— 52-53 (80) 47-49 (20) 32-33 (15)	1.1125 0.7719 0.7811 0.7739	1.6287 1.4428 1.4600 1.4518	93.99 42.63 48.47 48.17	2.2835 2.2837 2.2836 2.2834	0.547 0.160 0.276 0.108	1.1368 1.1367 1.1370 1.1368	-0.238 0.156 0.146 0.158	109.20 51.81 60.24 56.33
$(CH_3)_3Si-C\equiv C-C=CH$	107.5-108 (20)	0.8616	1.4940	60.25	2.2835	0.608	1.1369	0.018	81.86
$(C_6H_5)_3Si-C\equiv C-CH=CH_2$	—	1.0660	1.6579	105.26	2.2835	0.540	1.1369	-0.216	116.82

acetylene. At the same time, the introduction of a methyl radical into the 4-position leads to an increase in the dipole moment. This influence of methyl groups may be explained by means of the assumption that the moments of the conjugated system and the methyl radicals have opposite directions in the first case and the same direction in the second case [4].

From the data given in Table 1 and obtained earlier on the dipole moments of enyne hydrocarbons with a tertiary butyl radical, it follows that the substitution of a methyl group by a tertiary butyl group in the 1 or 3 position has little effect on the value of the moment. On the introduction of a methyl group into the 3 position of the molecule of vinyl-*t*-butylacetylene, the moment increases somewhat, just as it rises when a methyl group is introduced into the same position of the molecule of vinylmethylacetylene [5]. Possibly a change in the direction of the dipole moment takes place here.

When a triphenylmethyl radical is introduced into the molecule of vinylacetylene in place of hydrogen in the 1 position, the dipole moment increases, in comparison with that for vinylacetylene. Obviously, the phenyl ring is enriched with electrons at the expense of the enyne system. The reduction of the rate of addition of bromine to this hydrocarbon favors this hypothesis [7].

The same laws as in the case of hydrocarbons are observed in the enyne silicohydrocarbon series.

The replacement of a hydrogen atom in the molecule of vinyltrimethylsilylacetylene by a methyl group in the 3 position leads to a reduction, and in the 4 position to an increase, in the dipole moment in comparison with the initial compound. On replacing the trimethylsilyl group by a triphenylsilyl group, the dipole moment rises, approaching the value for the moment of unsubstituted vinylacetylene. Obviously, in this case also, phenyl rings play the role of electron acceptors. This supposition is confirmed by the chemical properties of vinyltriphenylsilylacetylene: on bromination it first reacts in respect of the phenyl rings and adds bromine with difficulty [2].

As a rule, enyne silicohydrocarbons have lower dipole moments than hydrocarbons. A similar situation exists in respect of a comparison of the dipole moments of, for example, trialkylhalogenosilanes and trialkylsilanols with the moments of the corresponding tertiary halogeno derivatives and alcohols [6]. This diminution in the value of the dipole moments on passing from carbon compounds to silicon compounds is generally explained by a displacement of the free electron pairs of the halogens or oxygen in the direction of the silicon atom, which has an unfilled *d* shell, i.e., by a partial double-bond character of the atoms or functional groups linked to the silicon atom [6]. It would seem that, in our case, such a displacement of the electron cloud of the conjugated system should lead to an increase in the dipole moment; however, in actual fact, the moment decreases.

Apparently, the direction of the dipole moment in the molecules of enyne silicohydrocarbons does not differ from its direction in the molecules of the corresponding hydrocarbons.

#### EXPERIMENTAL PART

The enyne hydrocarbons for the present work were prepared by various methods: vinyl-*t*-butylacetylene—by the alkylation of vinylacetylenylmagnesium bromide with *t*-butyl bromide [8]; isopropenyl-*t*-butylacetylene—by the dehydration of the alcohol obtained from *t*-butyl-acetylenylmagnesium bromide and acetone [8]; and triphenylmethyl-vinylacetylene—by the action of triphenylchloromethane on vinylacetylenylmagnesium bromide [7].

In the majority of cases, the enyne silicohydrocarbons were prepared by the action of trimethyl- or triphenyl-halogenosilanes on vinylacetylenylmagnesium bromide [2].

The constants of the compounds used in the investigation are given in Table 2.

The dipole moments were determined by the method of dilute solutions. The dielectric permeability was measured in an apparatus specially constructed for this purpose by the method of beats.

The measurements were carried out in benzene solutions at 20°C with concentrations of the order of 1, 1.5, 2, 4, and 5%. In the case of the silicohydrocarbons, scatter of the points was observed at higher concentrations.

It was shown in the investigations of Ya. K. Syrkin et al. that it is impossible to neglect atomic polarization in the case of silicon compounds [9]. For the silicohydrocarbons, the atomic polarization generally amounts to about 5 units per atom of silicon. We used this value in the present work.

The results of the investigations are given in Table 2.

#### SUMMARY

1. The dipole moments of four enyne hydrocarbons with tertiary butyl and triphenylmethyl radicals and of five enyne silicohydrocarbons with trimethylsilyl groups attached to a carbon atom of the triple bonds have been measured.

2. It has been established that the same laws apply in the enyne silicohydrocarbon series with respect to the change in the value of the dipole moments when methyl groups are introduced into different positions of the conjugated system as in the enyne hydrocarbon series.

3. The replacement of a carbon atom by silicon leads to some diminution in the dipole moments.

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## INVESTIGATIONS IN THE FIELD OF CONJUGATED SYSTEMS

### CXLIX. SYNTHESIS AND PROPERTIES OF HOMOLOGS

#### OF ALLYLVINYLACETYLENE\*

A. A. Petrov, Yu. I. Porfir'eva, K. S. Mingaleva,  
and N. I. Svetlova

Lensovet Leningrad Technological Institute

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A study of the addition reactions of divinylacetylene and its homologs has permitted a series of laws to be developed. It has been shown, for example, that alkyl hypobromites add to propenyl- and isopropenylvinylacetylenes at different double bonds. To the least substituted in the case of the first hydrocarbon and to the most substituted in the case of the second hydrocarbon [1, 2]. At the same time, alkylolithiums add to the least substituted vinyl group in both bases [2, 3]. The addition of water under the conditions of Kuchero's reaction takes place at the triple bond, vinylisopropenylacetylene giving a 2-methylhexadiene-3-one, and not a 2-methylhexadiene-4-one, the formation of which should have been expected according to the theory of electron displacements [4].

It was of interest to supplement these results by results on the reactivity of the double bonds in such compounds as allylvinylacetylene having one of them in an unconjugated position with respect to the 1,3-enyne system.

Allylvinylacetylene was prepared earlier by the action of allyl bromide on vinylacetylenylmagnesium bromide [5]. We attempted to extend this method to the synthesis of other similar alkenylvinylacetylenes.

Allyl bromide does not possess an allylic isomer, and therefore its reaction with vinylacetylenylmagnesium bromide can lead to the production of only one dienyne hydrocarbon. The homologs of allyl bromide, in the majority of cases, tend to undergo the allylic rearrangement and exhibit dual reactivity in reactions with various reagents. Hence, with vinylacetylenylmagnesium bromide, they may give a mixture of the dienyne hydrocarbons corresponding to the two possible isomers of the halogen derivative.

Literature data on the reactions of allyl halogen derivatives with the simplest organomagnesium compounds indicate that they generally lead to a mixture of the possible isomers with the predominance of the hydrocarbons corresponding to the more stable form of the halogen derivative [6-9]. With respect to the organomagnesium compounds of the acetylene series, this question has not been investigated by the necessary method [10].

We have studied the reaction of vinylacetylenylmagnesium bromide with crotonyl bromide, 3-methylbut-2-enyl bromide, and 2-bromopent-3-ene. In the first case, octa-1,6-dien-3-yne and 5-methylhepta-1,6-dien-3-yne may be obtained, in the second case 7-methylocta-1,6-dien-3-yne and 5,5-dimethylhepta-1,6-dien-3-yne, and in the third case only 5-methylocta-1,6-dien-3-yne.

The structure of the hydrocarbons actually obtained was shown by the method of hydrogenation to well-studied saturated hydrocarbons (comparison of the infrared spectra of the hydrogenation products with the spectra of known samples of the saturated hydrocarbons and mixtures of them).

Hydrogenation of the product of the reaction of crotonyl bromide with vinylacetylenylmagnesium bromide yielded predominantly normal octane with an admixture of 10-12% of 3-methylheptane. The infrared spectrum of the hydrogenation products coincided well with the spectrum of a known mixture containing the indicated amounts of n-octane and 3-methylheptane (Fig. 1, curve 1). The frequencies of 964, 995, 1145, and 1154  $\text{cm}^{-1}$ , which are absent or less intense in the spectrum of n-octane, were convenient for detecting the 3-methylheptane.

\* Dienynes. VI.



Hydrogenation of the product of the interaction of 3-methylbut-2-enyl bromide with vinylacetylenylmagnesium bromide yielded 2-methyloctane, in which no admixture of 3,3-dimethylheptane could be detected by the above

method using infrared spectroscopy. The spectrum of the hydrocarbon which we obtained coincided completely with the spectrum of a known sample of 2-methyloctane (Fig. 1, curve 4).

On hydrogenating the reaction product of 2-bromopent-3-ene with vinylacetylenylmagnesium bromide, as was to be expected, only 4-methyloctane was obtained (Fig. 1, curve 5).

Thus, it has been established that in the case of crotonyl bromide, which may be a source of either a primary or a secondary radical, the hydrocarbon obtained corresponded predominantly to the more stable primary form of the halogen derivative, although the other isomer was present. However, in the case of 3-methylbut-2-enyl bromide, which is capable of giving a primary or a tertiary radical, the isomer corresponding to the more stable primary form of the halogen derivative was obtained exclusively or almost exclusively.

This behavior may be due to two causes. In the first place, the great difference in stability of the secondary and tertiary cations formed at the moment of reaction, in comparison with the primary cation, is shown. In the second place, in the case of the tertiary cation, a well-known role may be played by steric hindrance.

The infrared spectra were investigated and the dipole moments were determined for all the hydrocarbons obtained.

The infrared spectra confirmed the positions of the multiple bonds in the molecules of all the compounds obtained which we assumed from the method of synthesis.

The infrared spectrum of allylvinylacetylene possessed two intense frequencies of the stretching vibrations of conjugated ( $1605\text{ cm}^{-1}$ ) and unconjugated ( $1635\text{ cm}^{-1}$ ) double bonds and the two frequencies of CH deformation vibrations ( $968$  and  $985\text{ cm}^{-1}$ ) correspond to the two different vinyl groups. An intense frequency at  $2222\text{ cm}^{-1}$  corresponded to the acetylenic bond. This bond is undoubtedly conjugated with only one vinyl group, since completely conjugated dienes absorb at  $2200\text{ cm}^{-1}$  (Fig. 2, curve 1) [1, 2].

In the case of crotonylvinylacetylene, only the frequency of the stretching vibrations of the conjugated double bond ( $1604\text{ cm}^{-1}$ ) is clearly shown in the infrared spectrum. The frequencies of the nonconjugated double bond in the *cis* and *trans* isomers of the hydrocarbon have a very low intensity ( $1645$  and  $1678\text{ cm}^{-1}$ ). In the  $900$ – $1000\text{ cm}^{-1}$  region, one of the deformation frequencies of the vinyl group ( $970\text{ cm}^{-1}$ ) and the expected frequency for the  $-\text{CH}=\text{CH}-$  group (about  $960\text{ cm}^{-1}$ ) are superimposed upon one another and give an intense band with a frequency of  $968\text{ cm}^{-1}$  (Fig. 2, curve 2).

The same features are characteristic for the infrared spectrum of 5-methylocta-1,6-dien-3-yne (Fig. 2, curve 4).

The frequency of the stretching vibrations of the unconjugated double bond ( $1680\text{ cm}^{-1}$ ) in the infrared spectrum of 3-methylbut-2-enylvinylacetylene also has a low intensity. The conjugated vinyl group is characterized by the usual stretching and deformation frequencies. The  $>\text{C}=\text{CH}-$  group is represented by a fairly intense frequency at  $840\text{ cm}^{-1}$  (Fig. 2, curve 3).

The dipole moment of allylvinylacetylene proved to be somewhat lower than that of propylvinylacetylene ( $0.65\text{ D}$ ) [11, 12]. Thus, an allyl radical in the first position decreases the polarity of the 1,3-enyne system to a greater extent than saturated radicals.

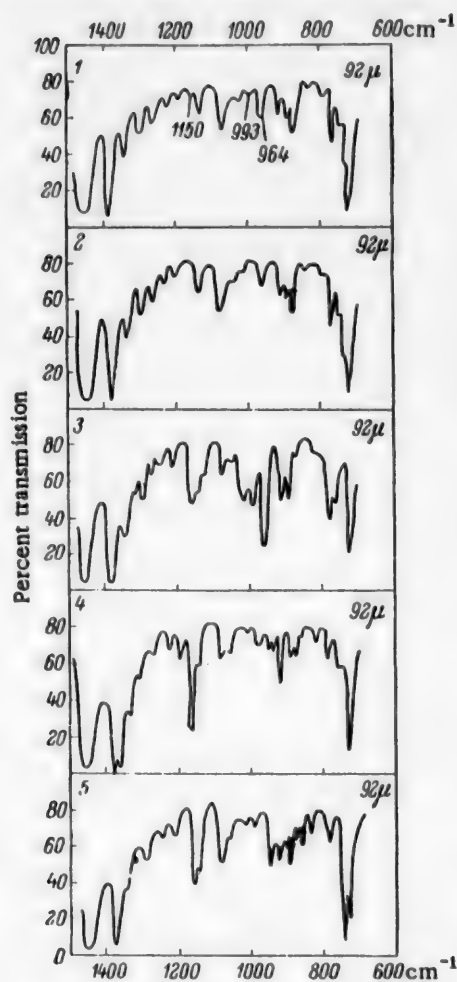


Fig. 1. Infrared transmission spectra. 1) Products of the hydrogenation of crotonylvinylacetylene, 2) *n*-octane, 3) 3-methylheptane, 4) products of the hydrogenation of 3-methylbut-2-enylvinylacetylene (2-methyloctane), 5) products of the hydrogenation of 5-methylocta-1,6-dien-3-yne (4-methyloctane).

In proportion as the hydrogen atoms of the allyl radical on the extreme carbon atom are replaced by methyl groups, the polarity of the dienyne hydrocarbons rises. Crotonylvinylacetylene already has a higher moment than vinylbutylacetylene (0.63 D) and, all the more, than isopropenylvinylacetylene (0.51 D)\* [13, but, however, less than propenylvinylacetylene (0.78 D); the dipole moment of 3-methylbut-2-enylvinylacetylene is even higher.

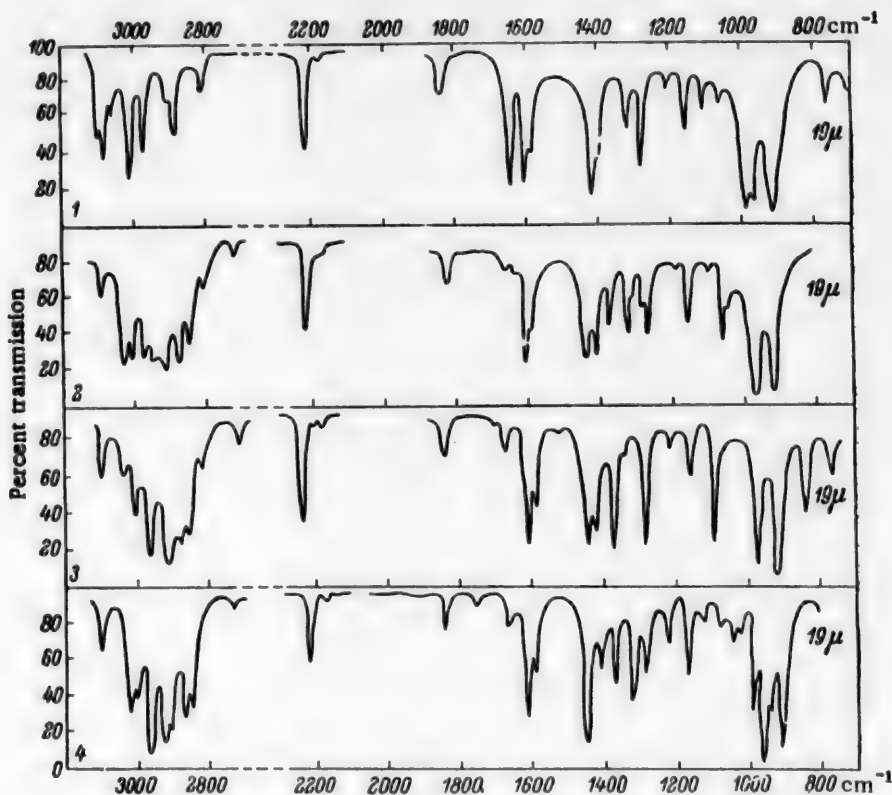


Fig. 2. Infrared transmission spectra. 1) Hepta-1,6-dien-3-yne; 2) octa-1,6-dien-3-yne (containing 5-methylhepta-1,6-dien-3-yne; 3) 7-methylocta-1,6-dien-3-yne; 4) 5-methylocta-1,6-dien-3-yne.

This increase in the dipole moment with substitution becomes comprehensible only if a change in the direction of polarization of the 1,3-enyne system is admitted.

The dipole moment of the isomer of 3-methylbut-2-enylvinylacetylene, 5-methylocta-1,6-dien-3-yne, in the molecule of which only one of the methyl groups is conjugated with the double bond, has the same value as the dipole moment of crotonylvinylacetylene.

It is interesting to compare these results on dipole moments with the results on the direction of the electrophilic and nucleophilic addition reactions of the dienyne hydrocarbons investigated, and we propose to do this subsequently.

#### EXPERIMENTAL PART

Commercial allyl bromide was distilled through a column before use. Crotonyl bromide, 3-methylbut-2-enyl bromide, and 2-bromopent-3-ene were prepared by the addition of hydrogen bromide to divinyl, isoprene, and perylene, respectively, in acetic acid. They were also distilled through a Widmer column.

\* This comparison is not completely accurate, since propenyl- and crotonylvinylacetylenes may contain the cis and trans isomers in different amounts.

The production of the dienyne hydrocarbons was carried out under conventional conditions: the bromides were slowly added to a 10-15% excess of vinylacetylenylmagnesium bromide in ether with intense stirring and cooling. Cuprous bromide was used as the catalyst. After they had stood for some hours, the cooled mixtures were treated with dilute sulfuric acid. The ethereal solutions of the hydrocarbons were separated, dried over  $\text{CaCl}_2$ , and subjected to distillation in a Widmer fractionating column.

TABLE 2. Infrared spectra of Allylvinylacetylene and its Homologs

Allylvinyl- acetylene	Crotonylvinyl- acetylene	3-Methylbut- 2-enylvinylene	5-Methylocta- 1,6-dien-3-yn
759 weak	772 very weak	768 weak	—
—	—	840 medium	—
919*	915 •	919 •	915 •
—	—	—	936 weak
970 strong	965 •	973 strong	965 •
991 strong	—	—	991 medium
1065 weak	1056 medium	—	1026-1055 weak
1105 medium	1103 weak	1096 strong	1130 ••
1162 medium	1160 medium	1156 medium	1174 medium
1210 weak	1192 ••	1215 ••	1236 weak
—	1270 medium	—	—
1286 strong	1286 weak	1287 strong	1290 medium
—	1307 ••	1305 ••	—
1323 medium	1325 medium	1322 ••	1327 medium
—	1376 medium	1376 strong	1375 medium
1420 •	1415 medium	1420 strong	1412 medium
—	1440 medium	1445 strong	1451 strong
1597 weak	1588 weak	1590 medium	1595 medium
1613 strong	1604 medium	1609 strong	1610 strong
1645 strong	1645 ••	—	—
—	1678 ••	1670 weak	1665 weak
1843 weak	1830 weak	1840 weak	1840 weak
2228 strong	2222 medium	2224 strong	2222 medium
—	2720 ••	2725 ••	2730 weak
2811 weak	2808 weak	2822 weak	—
—	2850 medium	2850 strong	2855 strong
2887 strong	2875 strong	2870 strong	2870 •
2907 weak	2910 •	2917 •	2915 strong
—	—	—	2930 strong
2982 strong	2955 strong	2966 strong	2970 •
3010 •	3003 strong	3005 strong	3008 strong
—	3022 strong	3035 medium	3029 strong
3085 strong	3092 medium	3095 medium	—
3100 medium	—	—	3100 medium

- Very Strong.
- Very weak

The constants and analytical data for the hydrocarbons obtained are given in Table 1.

The infrared spectra were taken on a IKS-15 spectrophotometer. The results are given in Fig. 2 and Table 2.\*

The initial data for the determination of the dipole moments are given in Table 3. The measurements were carried out in benzene at 20° by the method of beats. Atomic polarization was not taken into consideration.

TABLE 3. Data for the Determination of Dipole Moments

Substance	$\nu_1$	$\nu_2$	$\alpha$	$\beta$	$P_{\infty}$	$MR_D$
$\text{CH}_2=\text{CH}-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}=\text{CH}_2$	2.2834	1.1368	0.232	0.124	38.77	32.74
$\text{CH}_2=\text{CH}-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_3$	2.2836	1.1370	0.298	0.118	45.79	37.62
$\text{CH}_2=\text{CH}-\text{C}\equiv\text{C}-\text{CH}_2-\text{CH}=\text{C}(\text{CH}_3)_2$	2.2834	1.1368	0.788	0.096	61.99	42.38
$\text{CH}_2=\text{CH}-\text{C}\equiv\text{C}-\underset{\text{CH}_3}{\underset{ }{\text{CH}}}-\text{CH}=\text{CH}-\text{CH}_3$	2.2837	1.1368	0.314	0.128	52.55	42.50
$\text{CH}_2=\text{CH}-\text{C}\equiv\text{C}-\text{CH}=\text{CH}-\text{CH}_3$	2.2830	1.1370	0.760	0.112	47.48	34.57

TABLE 4. Constants of the Hydrogenation Products and Reference Materials

Substance	Boiling point (pressure in mm)	$d_4^{20}$	$n_D^{20}$
Hydrogenation product from crotonyl- vinylacetylene	122-124° (740)	0.7023	1.3995
n-Octane	123-124 (740)	0.7017	1.3990
3-Methylheptane	117-118 (740)	0.7054	1.4000
Hydrogenation product from 3-methyl- but-2-enylvinylacetylene	141-142 (736)	0.7124	1.4048
2-Methyloctane	141-142 (736)	0.7124	1.4048
3,3-Dimethylheptane**	137 (760)	0.7256	1.4088
Hydrogenation product from 5-Methyl- octa-1,6-dien-3-yne	141-142 (758)	0.7196	1.4068
4-Methyloctane	141-142 (758)	0.7196	1.4068

Hydrogenation was carried out over Pd/CaCO<sub>3</sub> in methanol. The hydrocarbons were distilled with steam, salted out with a saturated solution of CaCl<sub>2</sub>, washed with concentrated sulfuric acid, and distilled. The yield was about 89%. The constants of the saturated hydrocarbons obtained are given in Table 4. The same Table gives the constants of authentic n-octane, 3-methylheptane, 2-methyloctane, and 4-methyloctane. They all agree with data in the literature [14].

Commercial octane was used. The 3-methylheptane was prepared by hydrogenating the hydrocarbon formed in the dehydration of methyl ethyl butyl carbinol with a crystal of iodine. The carbinol was obtained by the action of butylmagnesium chloride on methyl ethyl ketone (chemically pure). The 2-methyloctane was prepared in a similar manner from dimethyl hexyl carbinol, obtained by the action of methylmagnesium bromide on methyl hexyl ketone (chemically pure). Methyl propyl butyl carbinol, obtained from methyl butyl ketone (pure) and propylmagnesium bromide, was used as the starting material for the preparation of the 4-methyloctane.

\*The infrared spectra were taken by T. V. Yakovleva and I. G. Savich.

\*\* Literature data [14].

## SUMMARY

1. Three homologs of allylvinylacetylene—octa-1,6-dien-3-yne (containing 5-methylhepta-1,6-dien-3-yne), 7-methylocta-1,6-dien-3-yne, and 5-methylocta-1,6-dien-3-yne—have been obtained and characterized.

2. It has been established that the dipole moments of the above hydrocarbons increase with the replacement of the hydrogen atoms and the terminal allyl carbon atom by methyl groups.

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# INVESTIGATIONS IN THE FURAN SERIES

## XIX. REACTION OF 2-ALKENYLFURANES WITH $\alpha$ , $\beta$ -UNSATURATED KETONES

Yu. K. Yur'ev, N. S. Zefirov, and V. M. Gurevich

M. V. Lomonosov Moscow State University

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 11,

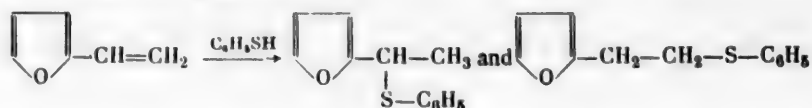
pp. 3531-3534, November, 1961

Original article submitted December 16, 1960

In recent times, much attention has been paid to bifunctional derivatives of furan [1, 2], and to the study of unsaturated compounds of the furan series, mainly their capacity for polymerization [3, 4].

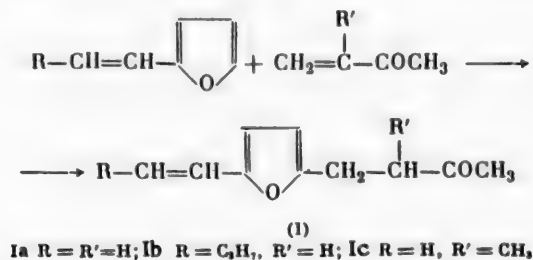
However, bifunctional derivatives of furan and, in particular, those containing a double or triple bond in one side chain together with a functional group in another are rather difficult to obtain. In view of this, it seemed of interest to us to use the comparatively readily obtainable 2-vinylfuran and its homologs for the synthesis of this type of compound.

The reactions of 2-vinylfuran with the exception of polymerization, have been far from fully studied. Thus, it is known, that it adds to the double bond of tetrafluoroethylene, forming furyltetrafluorocyclobutane [5], that bromination of 2-vinylfuran proceeds normally but the dibromide formed is unstable on storage [6], and that it is impossible to obtain the epoxide by the action of monoperphthalic acid [7]. We have shown that the reaction of radical addition to the double bond of 2-vinylfuran may take place: on allowing an equimolecular mixture of 2-vinylfuran with thiophenol to stand, the product of 1 : 1 addition is obtained with a quantitative yield, its structure corresponding to one of the sulfide structures given below.



It is also known from the literature that 2-vinylfuran forms an adduct with maleic anhydride—the anhydride of 4,5,6,9-tetrahydrobenzofuran-4,5-dicarboxylic acid—and thus the conjugated diene system formed by the double bonds of the side chain and the ring exhibit a higher reactivity than the diene system of the bonds of the furan ring [8, 9]. However, we have established that 2-vinylfuran does not react even with methyl maleic anhydride and therefore it may be expected that the reaction of 2-vinylfuran and its homologs with less active dienophiles, such as  $\alpha$ ,  $\beta$ -unsaturated ketones, will proceed more readily in the direction of a substitutive addition than in the direction of the diene synthesis [10, 11].

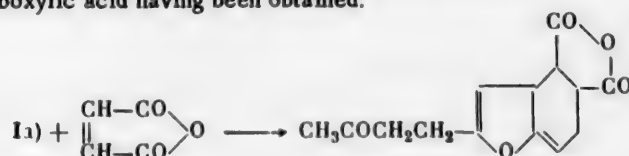
In actual fact, 2-vinylfuran reacts with methyl vinyl ketone in the presence of catalytic amounts of sulfuric acid with the formation of 1-(5-vinylfuran-2-yl)-butan-3-one:



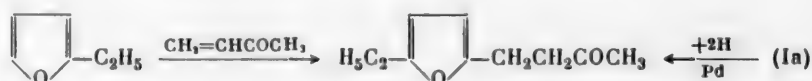


The reaction is accompanied by secondary polymerization processes in consequence of which the yield of ketone amounts to 20% (on heating the mixture in the absence of a catalyst, only polymerization products are obtained).  $\alpha$ ,  $\beta$ -Unsaturated ketones with a substituted vinyl group may take part in this reaction, as shown by the example of the reaction of 2-vinylfuran with methyl isopropenyl ketone. The homologs of 2-vinylfuran, as, for example, 2-pentenylfuran, react with methyl vinyl ketone according to the same scheme. In spite of the low yield, the reaction that we describe is the only convenient method for the synthesis of these ketones of the furan series. The ketones which we obtained consist of colorless liquids which rapidly turn yellow, with a pleasant floral odor. Our attempts to use 2-furylacetylene in the same reaction met with no success—only resinification took place.

Using 1-(5-vinylfur-2-yl)-butan-3-one (Ia) as an example, we have shown that ketones of this type, like 2-vinylfuran readily give adducts on reaction with maleic anhydride, the anhydride of 2-(3-oxobutyl)-4,5,6,9-tetrahydrobenzofuran-4,5-dicarboxylic acid having been obtained.



In the literature [12, 13] it is mentioned that the selective hydrogenation of the double bond in the side chain of 2-vinylfuran is associated with difficulties. We found, however, that in the presence of palladium on barium sulfate [14], the hydrogenation of the double bond in the side chain of 1-(5-vinylfur-2-yl)-butan-3-one (Ia) takes place smoothly and leads to 1-(5-ethylfur-2-yl)-butan-3-one (II), which proved to be identical with the compound obtained from 2-ethylfuran and methyl vinyl ketone.



## EXPERIMENTAL PART

**2-Vinylfuran.** A mixture of 520 g of malonic acid, 480 g of furfural, and 0.4 ml of quinoline was placed in a three-necked flask with a stirrer and heated on the water bath for 8 hours until the evolution of carbon dioxide ceased. Then 1-1.2 of quinoline was added and the mixture was slowly heated to 200° and cooled to 150°, 70 g of anhydrous copper sulfate and 2-3 g of hydroquinone were added, the flask was provided with a fractionating column with a downward condenser and, by strong heating, the vinylfuran and a small amount of water were distilled off. The vinylfuran was washed repeatedly with a 1 N caustic soda solution, and with water, dried with calcium chloride, and distilled under slightly reduced pressure in a current of nitrogen. Yield 180-190 g (40%).

B.p. 98-99° (760 mm),  $n_D^{20}$  1.4880,  $d_4^{20}$  0.9266,  $MR_D$  29.26.  $C_6H_6OF_2$ . Calculated 27.95.

Literature data: b.p. 98-99.5° (750 mm),  $n_D^{20}$  1.4402,  $d_4^{20}$  0.9018 [13]; b.p. 98-99°,  $n_D^{20}$  1.4992,  $d_4^{20}$  0.9455 [6].

**Reaction of vinylfuran with thiophenol.** A mixture of 4.2 g of thiophenol and 3.8 g of 2-vinylfuran was allowed to stand in a closed vessel for some days until the smell of the starting materials had disappeared. The reaction product was distilled in vacuum. A yield of 7.5 g (92%) of the sulfide was obtained.

B.p. 146-148° (6 mm),  $n_D^{20}$  1.5811,  $d_4^{20}$  1.0017,  $MR_D$  60.88.  $C_{12}H_{12}OSF_2$ . Calculated 60.22.

Found %: C 70.86, 70.72; H 6.00, 6.09.  $C_{12}H_{12}OS$ . Calculated %: C 70.55; H 5.92.

**1-(5-Vinylfur-2-yl)-butan-3-one (Ia).** A mixture of 0.2 g of hydroquinone, 14 g of methyl vinyl ketone, and 2 drops of concentrated sulfuric acid was placed in a 50-ml three-necked flask with a thermometer, stirrer, and dropping funnel, and 14.1 g of 2-vinylfuran was added dropwise in such a way that the temperature did not rise above 25°. The mixture was stirred for a further 1 hour and was then diluted with ether, washed repeatedly with bicarbonate solution, and water, and dried with anhydrous magnesium sulfate. The ether was evaporated off, and the ketone distilled in a current of nitrogen. The yield was 5 g (20.5%) of a colorless liquid with a pleasant odor.

B.p. 109-110° (5 mm),  $n_D^{20}$  1.5171,  $d_4^{20}$  1.0301,  $MR_D$  48.22.  $C_{10}H_{12}O_2F_2$ . Calculated 46.39.

Found %: C 73.35, 73.21; H 7.39, 7.59.  $C_{10}H_{12}O_2$ . Calculated %: C 73.14; H 7.43.

The 2,4-dinitrophenylhydrazone was obtained and purified by the procedure of [11]; it formed yellow crystals with m.p. 130-131°.

Found %: C 55.87, 55.76; H 4.86, 4.69.  $C_{18}H_{16}O_6N_4$ . Calculated %: C 55.80; H 4.69.

Adduct of the ketone (Ia) with maleic anhydride. To a solution of 0.49 g of maleic anhydride in the minimum amount of absolute ether, 0.82 g of the ketone (Ia) was added. After 12-15 hours, white crystals precipitated; m.p. 110-111° (from benzene); on standing in air, the substance decomposed after some hours.

Found %: C 64.25, 64.14; H 5.22, 5.36.  $C_{14}H_{14}O_5$ . Calculated %: C 64.11; H 5.38.

2-Methyl-1-(5-vinylfur-2-yl)-butan-3-one (Ic). A yield of 5.1 g of (19%) of the substance (Ic) was obtained from 14.1 g of vinylfuran and 16.4 g of methyl isopropenyl ketone, as described above; it formed a colorless liquid with a pleasant smell.

B.p. 105-107° (9 mm),  $n_D^{20}$  1.5080,  $d_4^{20}$  1.0390,  $MR_D$  52.16.  $C_{11}H_{14}O_2F_2$ . Calculated 51.01.

Found %: C 74.38, 74.30; H 8.10, 8.00,  $C_{11}H_{14}O_2$ . Calculated %: C 74.15; H 7.90.

1-(5-Penten-1-furyl-2-yl)-butan-3-one (Ib). A yield of 6.8 g (23%) of a colorless liquid was obtained from 20.4 g of pentenylfuran and 14 g of methyl vinyl ketone by the above-described method [15].

B.p. 121-122° (5 mm),  $n_D^{20}$  1.5081,  $d_4^{20}$  1.0511,  $MR_D$  62.69,  $C_{13}H_{18}O_2F_2$ . Calculated 60.29.

Found %: C 75.31, 75.16; H 8.65, 8.66.  $C_{13}H_{18}O_2$ . Calculated %: C 75.67; H 8.00.

2,4-Dinitrophenylhydrazone—yellow crystals with m.p. 64° (from benzene).

Found %: C 58.80, 58.89; H 5.90, 6.04.  $C_{19}H_{22}O_6N_4$ . Calculated %: C 59.05; H 5.75.

2-Ethylfuran. A solution of 9.4 g of 2-vinylfuran in 50 ml of methanol was hydrogenated in the presence of 0.1 g of palladium on barium sulfate (5% Pd). After the absorption of an amount of hydrogen equivalent to one double bond, the hydrogenation ceased abruptly. Yield 8.7 g (90%).

B.p. 91.5-92° (752 mm),  $n_D^{20}$  1.4410,  $d_4^{20}$  0.9018.

Literature data: b.p. 91°,  $n_D^{20}$  1.4400 [14].

1-(5-Ethylfur-2-yl)-butan-3-one (II). (a) A solution of 3.5 g of compound (Ia) in 40 ml of methanol was hydrogenated as described above. Yield 2.95 g (81%).

B.p. 95° (5 mm),  $n_D^{20}$  1.4726,  $d_4^{20}$  0.9986,  $MR_D$  46.67.  $C_{10}H_{14}O_2F_2$ . Calculated 46.88.

Found %: C 72.23, 72.41; H 8.61, 8.64.  $C_{10}H_{14}O_2$ . Calculated %: C 72.25, H 8.49.

2,4-Dinitrophenylhydrazone—golden crystals with m.p. 110° (from alcohol).

Found %: C 55.32, 55.41; H 5.34, 5.40.  $C_{18}H_{18}O_6N_4$ . Calculated %: C 55.48, H 5.24.

b) Starting with 9.6 g of 2-ethylfuran and 10.5 g of methyl vinyl ketone in the presence of 0.15 ml of concentrated sulfuric acid, as described for 2-methylfuran [11], 8.6 g (52%) of compound (II), identical with the preceding preparation, was obtained. The dinitrophenylhydrazone and a mixture of it with the preceding preparation melted at 110°.

#### SUMMARY

The reaction of alkenylfurans with  $\alpha, \beta$ -unsaturated ketones in the presence of sulfuric acid takes place as a substitutive addition.

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# CHEMISTRY OF SELENOPHENE

## XXXIV. REDUCTION OF THE KETONES OF THE SELENOPHENE

### SERIES

Yu. K. Yur'ev and N. K. Sadovaya

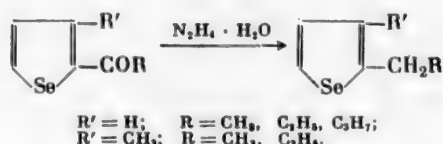
M. V. Lomonosov Moscow State University

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Original article submitted December 1, 1960

In our previous work on the production of the methyl homologs of selenophene [1, 2] we used reduction of a carbonyl group by N. M. Kizhner's general method [3] and a method described by one of us for the case of the reduction of selenophene-2-aldehyde [4]. We obtained 2,3-dimethylselenophene, the isomeric trimethylselenophenes, and tetramethylselenophene in this way. Continuing the study of the reactions of the ketones of the selenophene series, we have used the same method of reduction on some of them, and this has enabled us to synthesize the previously unreported 2-ethyl-, 2-propyl-, and 2-butylselenophenes, and also 2-ethyl-3-methyl- and 2-propyl-3-methylselenophenes, with yields of 48-80%.



Attempts to use Clemmensen's method and to carry out the reduction of the ketones with amalgamated zinc in hydrochloric acid were unsuccessful. Completeresinification of the reaction mixture took place.

### EXPERIMENT PART

A mixture of 0.08 g-mole of the ketone, 0.34 g-mole of hydrazine hydrate, and 0.25 g-mole of caustic soda in 100 ml of ethylene glycol was heated for 0.5 hour at 110-120°, and then for 1 hour at 170-180°. After replacing the reflux condenser by a downward condenser, all the material passing over up to 180° was distilled off. The distillate obtained was extracted with ether, and the extracts were washed with 2 N hydrochloric acid and water, and dried with calcium chloride. After distilling off the solvent, the reduction product was distilled.

**2-Ethylselenophene.** Starting with 14 g of 2-acetoselenophene (b.p. 104-105° at 11 mm,  $n_D^{20}$  1.5927 [5]), 16 g of 85% hydrazine hydrate, and 10 g of caustic soda, we obtained 10.1 g (79%).

B.p. 156.5-157.5° (753 mm),  $n_D^{20}$  1.5469,  $d_4^{20}$  1.3562,  $MR_D$  37.22.  $C_6H_6SeF_2$ . Calculated 37.88.

Found %: C 45.64; 45.46; H 5.30, 5.41; Se 49.35; 49.58.  $C_6H_6Se$ . Calculated %: C 45.29; H 5.07; Se 49.63.

**2-Propylselenophene.** Starting from 15 g of 2-propioselenophene (b.p. 110-111° at 10 mm,  $n_D^{20}$  1.5870 [6]), 16 g of 85% hydrazine hydrate, and 10 g of caustic soda, we obtained 6.6 g (48%).

B.p. 60-61° (15 mm),  $n_D^{20}$  1.5358,  $d_4^{20}$  1.2892,  $MR_D$  41.85.  $C_7H_{10}SeF_2$ . Calculated 42.00.

Found %: C 48.80, 48.82; H 5.89, 5.92; Se 45.28, 44.93.  $C_7H_{10}Se$ . Calculated %: C 48.57; H 5.82; Se 45.19.

**2-Butylselenophene.** Starting from 16 g of 2-butyroselenophene (b.p. 112-113° at 11 mm,  $n_D^{20}$  1.5732 [5]), 16 g of 85% hydrazine hydrate, and 10 g of caustic soda, we obtained 8.1 g (54%).

B.p. 75-76° (10 mm),  $n_D^{20}$  1.5267,  $d_4^{20}$  1.2392,  $MR_D$  46.43.  $C_8H_{12}SeF_2$ . Calculated 46.61.

Found %: C 51.88, 51.70; H 6.74, 6.83; Se 41.91, 42.31.  $C_9H_{12}Se$ . Calculated %: C 51.37; H 6.47; Se 42.21.

2-Ethyl-3-methylselenophene. Starting from 15 g of 3-methyl-2-acetoselenophene (b.p. 117-118° at 18 mm,  $n_D^{20}$  1.5941 [7]), 16 g of 85% hydrazine hydrate, and 10 g of caustic soda, we obtained 8.4 g (59%).

B.p. 70-71° (18 mm),  $n_D^{20}$  1.5429,  $d_4^{20}$  1.3049,  $MR_D$  41.81.  $C_7H_{10}SeF_2$ . Calculated 42.00.

Found %: C 48.69, 48.55; H 5.74, 5.72.  $C_7H_{10}Se$ . Calculated %: C 48.57; H 5.82.

2-Propyl-3-methylselenophene. Starting from 16 g of 3-methyl-2-propioselenophene (b.p. 38-39° [7]), 16 g of 85% hydrazine hydrate, and 10 g of caustic soda, we obtained 7.6 g (53%).

B.p. 68-69° (9 mm),  $n_D^{20}$  1.5356,  $d_4^{20}$  1.2582,  $MR_D$  46.34.  $C_9H_{12}SeF_2$ . Calculated 46.61.

Found %: C 51.26, 51.66; H 6.28, 6.37.  $C_9H_{12}Se$ . Calculated %: C 51.37; H 6.47.

#### SUMMARY

The reduction of the ketones of the selenophene series by Kizhner's general method may be successfully used for the production of alkylselenophenes.

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# SYNTHESIS OF HETEROCYCLIC ANALOGS OF STILBENE

Yu. K. Yur'ev and D. Ékkhardt

Moscow State University

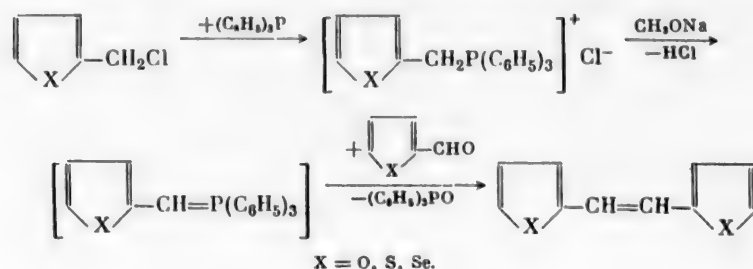
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 11,

pp. 3536-3539, November, 1961

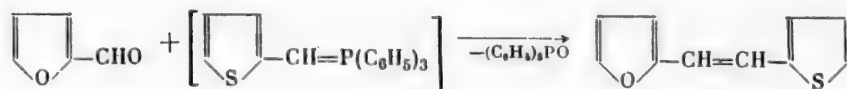
Original article submitted December 1, 1960

Only isolated cases of the production of heterocyclic analogs of stilbene have been described in the literature. Thus, in the thermal decomposition of thiofurfural, and tris-(thiofurfural), 1,2-di-(fur-2-yl)-ethylene was obtained, though in poor yields [1-3]; the thermal decomposition of furfuralazine gives better results, but the yield does not exceed 15% [4]. 1,2-Di-(thien-2-yl)-ethylene was obtained in a similar way—by the thermal decomposition of tris-(thiophene-2-thioaldehyde) in the presence of copper [5], and also in the pyrolysis of 2-chloro-1,1-di-(thien-2-yl)-ethane [6]; the yields were small in both cases.

Since Wittig's reaction has been used in a number of investigations [7-12] for the synthesis of derivatives of stilbene and alkenylbenzenes, it appeared of interest to study the possibility of using it for the production of 1,2-disubstituted ethylenes with heterocyclic radicals. In this synthesis, we carried out the preparation of a phosphonium salt containing a furfuryl, thenyl, or selenenyl radical by the reaction of the 2-chloromethyl derivative of furan, thiophene, or selenophene respectively, with an excess of triphenyl phosphite (in order to avoid resinification) in benzene or toluene with heating; on purifying these salts by reprecipitation from methanol, solvation of them is possible. By subsequently eliminating hydrogen chloride from the phosphonium salts by the action of sodium methoxide as proposed in [11], and the reaction of the "ylenes" formed with the appropriate heterocyclic aldehydes, we obtained 1,2-di-(fur-2-yl)-ethylene (49%), 1,2-di-(thien-2-yl)-ethylene (50%), and 1,2-di-(selenien-2-yl)-ethylene (44%).



This method also enables unsymmetrical heterocyclic analogs of stilbene to be obtained: by the reaction of triphenylphosphine-2-thenal with furfural in the presence of sodium methoxide we obtained 1-(fur-2-yl)-2-(thien-2-yl)-ethylene (35%).



## EXPERIMENTAL PART

**1,2-Di-(fur-2-yl)-ethylene.** (a) A solution of 8.5 g of 2-chloromethylfuran (b.p. 32-33° at 7 mm [14]) in 55 ml of benzene was added to 20 g of triphenylphosphine [13], and the mixture was boiled for 10 hours. The white precipitate of triphenylfurylphosphonium chloride was separated off, washed with absolute ether, and purified by reprecipitation from anhydrous methanol with absolute ether. Yield 20 g (70%); Decomp. p. 260°.



Found %: C 72.37, 72.43; H 5.34, 5.24; Cl 9.58; P 8.06,  $C_{23}H_{20}OClP$ . Calculated %: C 72.92; H 5.32; Cl 9.35; P 8.36.

(b) A mixture of 5 g of the phosphonium salt and 1.26 g of furfural in 15 ml of absolute methanol was placed in a three-necked flask with a reflux condenser, stirrer and dropping funnel, and boiled while 10.5 ml of a methanolic solution of 0.713 g of sodium methylate was added dropwise. The mixture became dark red, and gradually lightened and deposited a white precipitate. The mixture was boiled for a further 30 minutes, and was then cooled; the solution was separated off, and then the solvent was distilled off and the residue distilled with steam. The distillate was extracted with ether and the extracts were evaporated. The residue was crystallized from alcohol with activated carbon and sublimed in vacuum at 0.1 mm. Colorless needles. Yield 1.0 g (49%).

M.p. 99.5-100°.

Found %: C 75.15, 75.11; H 5.30, 5.10.  $C_{10}H_8O_2$ . Calculated %: C 75.00; H 5.00.

Literature data: m.p. 98° [1]; m.p. 101° [2].

1,2-Di-(thien-2-yl)-ethylene. (a) A mixture of 5 g of 2-chloro-methylthiophene (b.p. 76-80° at 9 mm [15]) in 50 ml of absolute benzene and 12.3 g of triphenylphosphine was boiled for 15 hours, and then the benzene was replaced with toluene and boiling was continued for a further 30 minutes. After working up the residue as described above, 10.7 g (79%) of triphenyl-2-thenylphosphonium chloride was obtained.

M.p. 288-289°.

Found %: C 69.22, 69.43; H 5.25, 5.02; Cl 8.95, 8.99; P 7.65, 7.68.  $C_{23}H_{20}SClP \cdot CH_3OH$ . Calculated %: C 69.14; H 5.83; Cl 8.50; P 7.43.

The analytical results indicate the solvation of the salt by the methyl alcohol (1 : 1).

(b) A solution of 0.605 g of sodium methoxide in 10 ml of methanol was added dropwise, with boiling, to a mixture of 5 g of the phosphonium salt in 25 ml of anhydrous methanol and 1.45 g of thiophene-2-aldehyde in 17 ml of absolute ether, and the mixture was boiled for 1 hour and worked up as described above. After vacuum sublimation, a yield of 0.95 g (50%) was obtained. Colorless crystals.

M.p. 132-132.5°.

Found %: C 62.64, 62.41; H 4.23, 4.30.  $C_{10}H_8S_2$ . Calculated %: C 62.50; H 4.16.

Literature data: m.p. 125° [6]; m.p. 132.5° [5].

1,2-Di-(selenien-2-yl)-ethylene. (a) A mixture of 5.1 g of 2-chloromethylselenophene (b.p. 74-77° at 6 mm) in 50 ml of toluene and 10 g of triphenylphosphine was boiled for 7 hours. After working up the precipitate as described above, 7.5 g (52.5%) of triphenyl-(selenen-2-yl)-phosphonium chloride was obtained.

Decomp. p. 276°.

Found %: C 62.00, 61.80; H 4.72, 4.66; Cl 8.20, 8.23.  $C_{23}H_{20}ClPSe$ . Calculated %: C 62.53; H 4.56; Cl 8.02.

(b) A solution of 0.605 g of sodium methoxide in 10 ml of methanol was added to a mixture of 5.5 g of the phosphonium salt and 2.36 g of selenophene-2-aldehyde in 15 ml of anhydrous methanol, and the mixture was boiled for 1 hour and worked up as described above. Yield 1.5 g (44%). Yellowish crystalline powder.

M.p. 153-153.5°.

Found %: C 42.59, 42.55; H 3.27, 3.05.  $C_{10}H_8Se_2$ . Calculated %: C 41.98; H 2.82.

1-(Fur-2-yl)-2-(2-thienyl)-ethylene. A solution of 0.54 g of sodium methoxide in 7.8 ml of methanol was added to 4 g of triphenyl-2-phenylphosphonium chloride and 1.24 g of furfural in 15 ml of anhydrous methanol, as described above, the mixture was boiled for 40 minutes, and worked up as described above. Yield 0.45 (35%).

B.p. 79.5-80°.

Found %: C 67.90, 68.10; H 4.68, 4.56.  $C_{10}H_8OS$ . Calculated %: C 68.20; H 4.54.

## SUMMARY

The reaction of triphenylphosphinyl-2-furfural, -2-thenal, and -2-selenenal with furfural, thiophene-2-aldehyde, and selenophene-2-aldehyde, respectively, forms a convenient method for the synthesis of heterocyclic analogs of stilbene. In this way, 1,2-di-(fur-2-yl)-, 1,2-di-(2-thienyl)-, 1,2-di-(2-selenienyl)-, and 1-(fur-2-yl)-2-(2-thienyl)-ethylenes have been obtained.

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INVESTIGATION IN THE FIELD OF THE CHEMISTRY  
OF FREE RADICALS OF THE HYDRAZINE SERIES

V. SYNTHESIS OF  $\alpha,\alpha$ -DIPHENYL- $\beta$ -2,6-DINITROPHENYLHYDRAZYL  
AND  $\alpha,\alpha$ -DIPHENYL- $\beta$ -2,4-DINITROPHENYLHYDRAZYL AND THE STUDY  
OF THEIR CHEMICAL AND PHYSICAL PROPERTIES

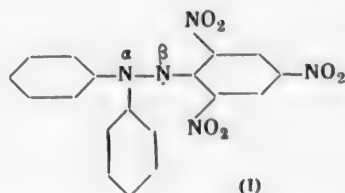
R. O. Matevosyan, M. A. Ikrina, and A. K. Chirkov

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 11,

pp. 3539-3544, November, 1961

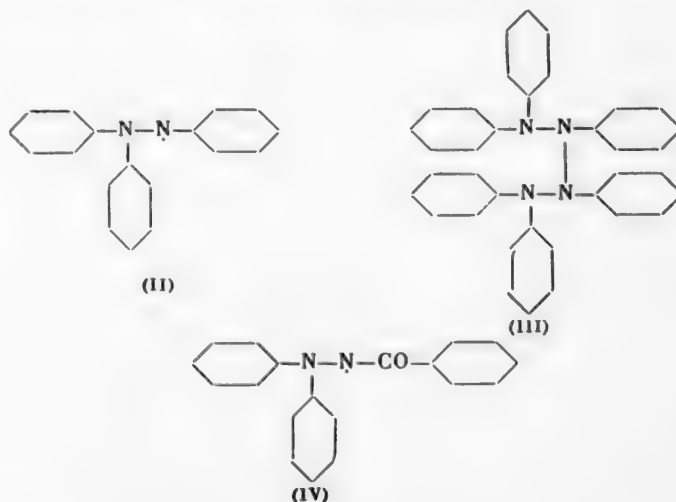
Original article submitted December 27, 1960

It was shown in previous communications [1] that the stability and exchange reactions of the unpaired electron of the  $\beta$ -nitrogen atom in diphenylpicrylhydrazyl (I) depended on the degree of delocalization of the unpaired electron of the  $\beta$ -nitrogen atom in the radical.



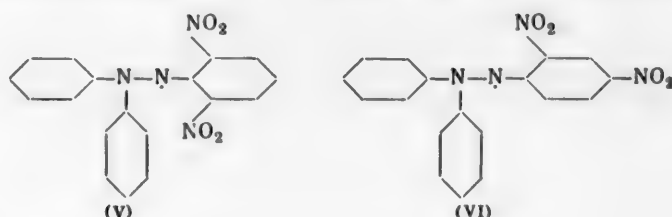
The greater the electron density on the  $\alpha$ -nitrogen atom, the greater the delocalization of the free electron of the  $\beta$ -nitrogen atom and the greater the stability of the radical. However, the cause of the stability of hydrazine radicals, in particular diphenylpicrylhydrazyl (I) must be sought not only in the diphenylamine but also in the trinitrophenyl part of the molecule.

It is known that  $\alpha,\alpha$ -diphenyl  $\beta$ -phenylhydrazine is converted to  $\alpha,\alpha$ -diphenyl- $\beta$ -phenylhydrazyl (II) on careful oxidation with lead dioxide. However, this radical is unstable on storage: All attempts to isolate it were unsuccessful, the dimer (III) always being obtained [2]. Replacement of the  $\beta$ -phenyl group in diphenylphenylhydrazyl by the benzoyl group (IV) did not lead to a radical of higher stability [3].

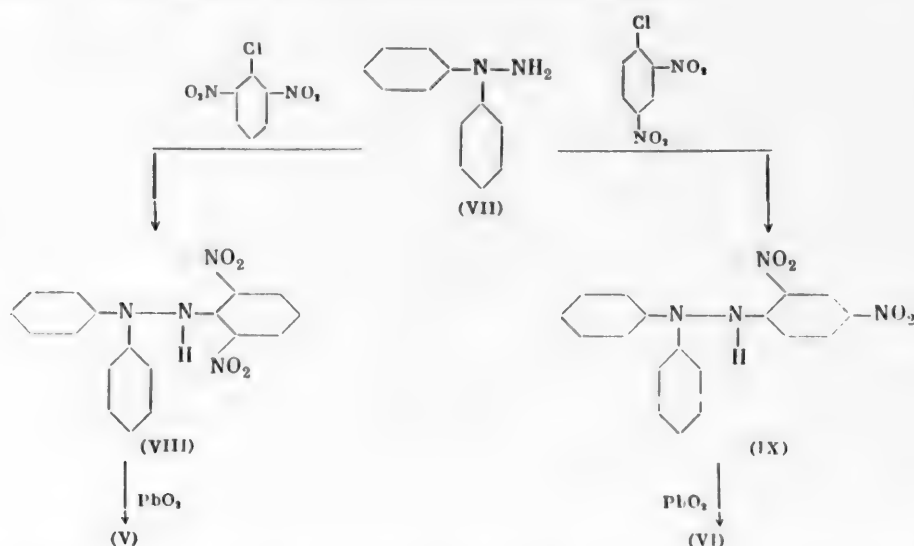


It might be supposed, from these results, that the stability of diphenylpicrylhydrazyl (I) was connected with the strong electronegative action of the picryl residue, stabilizing the free valency electron of the  $\beta$ -nitrogen atom by displacing the electron cloud in the direction of the trinitrophenyl group. However, the results of the superfine structure of the paramagnetic resonance absorption of diphenylpicrylhydrazyl in solution disprove this assumption: The electron cloud of the unpaired electron in the radical (I) is not displaced in the direction of the trinitrophenyl group and, in the main, is uniformly distributed between the  $\alpha$  and  $\beta$ -nitrogen atoms [4]. In view of this, an investigation of the influence of the trinitrophenyl group on the chemical and physical properties of diarylpicryl radicals may be of interest.

The object of the present investigation is the synthesis and investigation of the physicochemical properties of  $\alpha, \alpha$ -diphenyl- $\beta$ -2,6-dinitrophenylhydrazyl (V) and  $\alpha, \alpha$ -diphenyl- $\beta$ -2,4-dinitrophenylhydrazyl (VI)\*



The synthesis of these compounds was carried out by the following scheme.



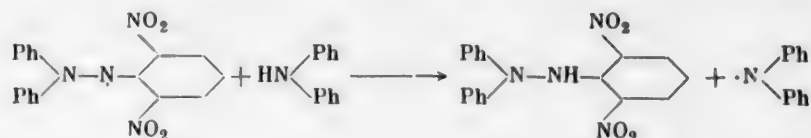
In distinction from picryl chloride, 2,6-dinitrochlorobenzene and 2,4-dinitrochlorobenzene react with diphenylhydrazine (VII) with great difficulty, the first being far more active than the second.

\* When the present work had been completed, we found a paper by Tyudesh et al. [13] in which results were reported of an investigation of the kinetics of the inhibition of the polymerization of styrene using the radical (V), the synthesis and further investigation of which the authors intend to report in one of their subsequent communications. Since the present paper is a continuation of our previous work and does not touch on the questions dealt with in the Hungarian authors' paper, we consider it proper to give the experimental data which we possess on the radicals (V) and (VI).

On shaking  $\alpha,\alpha$ -diphenyl- $\beta$ -2,4-dinitrophenylhydrazine (IX) with lead dioxide in anhydrous chloroform by the method described earlier, the red solution becomes dark violet, which indicates the formation of a free radical; however, on treating it with an alcoholic solution of hydroquinone, almost instantaneous reddening of the violet solution is observed. The solution yielded the initial hydrazine (IX), which, on re-treatment with lead dioxide in chloroform, became colored dark violet. However, we did not succeed in isolating the hydrazyl (VI) in crystalline form.

Thus, it is possible to state that  $\alpha,\alpha$ -diphenyl- $\beta$ -2,6-dinitrophenylhydrazyl (V) is considerably more stable than the isomeric  $\alpha,\alpha$ -diphenyl- $\beta$ -2,4-dinitrophenylhydrazyl (VI). The reason for this must be sought not only in the spatial structure of the dinitrophenyl residues, but also in the electronegative action of the 2,6- and 2,4-dinitrophenyl residues on the  $\beta$ -nitrogen atom. However, this question still requires special study.

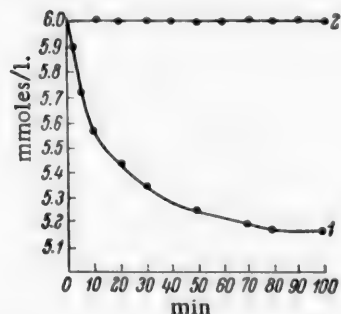
In order to compare the chemical and physical properties of the hydrazyl (V) with diphenylpicrylhydrazyl (I) the possibility of dehydrogenating diphenylamine by the radical (V) according to the equation



was investigated by the method of photocolormetry of mixtures of solutions of (V) with a solution of diphenylamine, and the electron paramagnetic absorption spectra in crystalline samples of this radical were taken.\*

The dehydrogenation of diphenylamine by the hydrazyl (V) was investigated in a PÉK-M photoelectric colorimeter, with a concentration of the radical of  $6 \cdot 10^{-2}$  mmole/l, a concentration of the diphenylamine of  $6 \cdot 10^{-1}$  mmole/l, a temperature of  $40^\circ$ , using a Vobzer thermostat, with chloroform as the solvent.

The results of the experiments showed (Figure), that (I) reacts with diphenylamine quite actively, while the hydrazyl (V) does not react, which, obviously, is due to the absence in it of a strong electron-acceptor group in position 4, which leads to a diminution in the electron-withdrawing effect of the dinitrophenyl group and an increase in the electron density on the  $\beta$ -nitrogen atom. The latter favors an increased coupling of the  $\alpha$  atom with the  $\beta$  atom and, consequently, a greater delocalization of the unpaired electron of the  $\beta$  atom.



Rate curves for the dehydrogenation of diphenylamine by diphenylpicrylhydrazyl (1) and diphenyldinitrophenylhydrazyl (2).

In other words, the free valency electron of the  $\beta$ -nitrogen atom in  $\alpha,\alpha$ -diphenyl- $\beta$ -2,6-dinitrophenylhydrazyl (V), on account of the greater electron density on the  $\beta$ -nitrogen atom and the greater degree of conjugation with the phenyl rings through the unshared pair (p) of electrons of the  $\alpha$ -nitrogen atom, in comparison with diphenylpicrylhydrazyl (I) is delocalized to a greater degree than in the radical (I), which also leads to an increased stability of (V) in comparison with (I).

On the basis of the investigation carried out, it may be assumed that the role of the picryl residue in the stability of diphenylpicrylhydrazyl (I) consists, on the one hand, in the steric hindrance of the dimerization reaction created by the nitro groups in the 2,6-positions; and, on the other hand, in the electron-withdrawing action of the unshared pair (p) of electrons of the  $\beta$ -nitrogen atom.

In conclusion, we shall give the results of measurements of the breadth of the line of electron paramagnetic resonance absorption in crystalline samples of the radical (V). For comparison, the results for diphenylpicrylhydrazyl (I) are also shown.

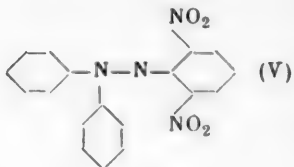
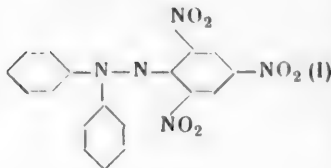
\* The EPR of the radical (V) was investigated by A. K. Chirkov.

The measurements were carried out in weak fields—20 oe—in the apparatus described earlier [8]. The breadth of the line of electron paramagnetic absorption characterizing the magnitude of the exchange interactions in crystal-line samples of the radical (V) is considerably greater than that of the line for diphenylpicrylhydrazyl (I). Thus, as in the previous cases, the more highly stabilized the radical, the broader the curve of paramagnetic resonance ab-sorption.

## EXPERIMENTAL PART

$\alpha,\alpha$ -Diphenylhydrazine (VII) was obtained by a reported method [5, 6]. By reducing N-nitrosodiphenylamine in acetic acid with zinc dust at 0–+5°, we succeeded in increasing its yield from 30–35 to 65–70%. The hydrazine

TABLE

Structure of the radical	Breadth of the line between the points of max. slope $\Delta H_M, N$
 (V)	$4.3 \pm 0.01$
 (I)	$1.0 \pm 0.01$

was distilled at 174–177° (10 mm) or 165–169° (5 mm). It formed a heavy pale yellow oil, crystallizing on standing; m.p. 43–44°. literature data[9]: m.p. 44°. On heating in alcoholic solution with p-nitrobenzaldehyde, the clear yellow crystalline hydrazone with m.p. 131–132.5° was formed in quantitative yield; literature [10]: m.p. 131°.

2,6-Dinitrochlorobenzene was obtained by Gunstone and Tucker's method [11] via 2,6-dinitroaniline; the latter was obtained by Schultz's method [12].

$\alpha,\alpha$ -Diphenyl- $\beta$ -2,6-dinitrophenylhydrazine (VIII). A mixture of 0.05 g-mole of diphenylhydrazine (VII), 0.025 g-mole of 2,6-dinitrochlorobenzene, and 0.01 g-mole of calcined sodium carbonate, after grinding in a mortar, was moistened with a small amount of alcohol and held in the fused state at 105–110° for 2 hrs. After the reaction mass had been cooled, it was treated with a small amount of concentrated hydrochloric acid and extracted with ether. After the removal of the ether by distillation, the residual dark red oil set to a monolithic mass, which crystallized from al-cohol in the form of coarse orange red prisms. Yield 30–35%; m.p. 140–141°.

Found %: C 61.41; H 4.18; N 16.06  $C_{18}H_{14}O_4N_4$ . Calculated %: C 61.71, H 4.00, N 16.00.

The product obtained is readily soluble in ether, benzene, acetone, chloroform, mineral acids, and acetic acids, and sparingly soluble in petroleum ether and cold alcohol.

$\alpha,\alpha$ -Diphenyl- $\beta$ -2,4-dinitrophenylhydrazine (IX) was obtained in a similar manner to the preceding compound. After removing the ether, the residual poorly-crystallizing dark red oil was treated with a large volume of hot alco-hol, which, on cooling, deposited orange red prisms, readily soluble in ether, benzene, acetone, chloroform, mineral acids, and acetic acid, and sparingly soluble in carbon tetrachloride, petroleum ether, and cold alcohol. Yield 30–35%; m.p. 120–121°.

Found %: C 61.44; H 4.11; N 15.76.  $C_{18}H_{14}O_4N_4$ . Calculated %: C 61.71; H 4.00; N 16.00.

$\alpha,\alpha$ -Diphenyl- $\beta$ -2,6-dinitrophenylhydrazyl (V). A large excess of lead dioxide and 0.004 g -mole of calcined sodium sulfate was added to 0.005 g-mole of the hydrazine (VIII) in dry chloroform. The reaction mixture was shaken for 2 hours, the dark violet solution was separated from the sludge, chromatographed on alumina, the chloroform was distilled off in vacuum, and the precipitate which formed was filtered off and dried in vacuum for 4–5 hours. The free radical formed black crystals with m.p. 169–170° (with decomp.). Yield 65–70%.

Found %: C 61.84; H 3.85; N 16.30.  $C_{18}H_{13}O_4N_4$ . Calculated %: C 61.89; H 3.72; N 16.05.

The product obtained is readily soluble in chloroform, benzene, toluene, xylene, and acetone with a dark vi-olet coloration, and in ether with a red coloration; it is sparingly soluble in alcohol. It dissolved in concentrated sulfuric acid with a green coloration, and in concentrated hydrochloric acid, glacial acetic acid, hydrobromic acid, nitric acid, 30% caustic soda and concentrated ammonia with a yellow coloration. No absorption of oxygen is ob-served in these solutions when a current of oxygen is passed through them or when they are allowed to stand for a long time under a pressure of oxygen. On reaction with an alcoholic solution of hydroquinone, the initial hydrazine (VIII) is rapidly re-formed.



$\alpha,\alpha$ -Diphenyl- $\beta$ -2,4-dinitrophenylhydrazyl (VI) was obtained in a similar manner to (V). In this process, the reddish orange chloroform solution becomes dark violet, but becomes orange again on reaction with an alcoholic solution of hydroquinone; the initial hydrazine was isolated quantitatively from this reduced solution. No crystalline product could be isolated.

We take this opportunity to express our thanks to Prof. I. Ya. Postovskii for the attention which he devoted to us in this investigation.

#### SUMMARY

1. The following radicals of the hydrazine series have been synthesized:  $\alpha,\alpha$ -Diphenyl- $\beta$ -2,6-dinitrophenylhydrazyl (V) and  $\alpha,\alpha$ -diphenyl- $\beta$ -2,4-dinitrophenylhydrazyl (VI).
2. It has been shown that the hydrazyl (V) is considerably more stable than hydrazyl (VI), evidently because of the screening of the  $\beta$ -nitrogen atom by the nitro groups in the 2,6-positions of the  $\beta$ -phenyl ring.
3. In studying the relative dehydrogenating power for diphenylamine of diphenylpicrylhydrazyl (I) and the diphenyldinitrophenylhydrazyl (V) it was shown that the radical (V) is considerably more stable than radical (I).
4. Considerations relating to the role of the picryl residue in the stability of diarylpicrylhydrazyl radicals have been expressed.
5. The electron paramagnetic absorption spectra have been determined for crystalline samples of the radical (V).

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# AMINO DERIVATIVES AND METHACRYLAMIDES FROM ACETALS OF XYLITOL AND XYLITAN\*

A. N. Anikeeva, T. I. Orlova, and S. N. Danilov

Institute of High Molecular Weight Compounds of the Academy  
of Sciences of the USSR

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 11,

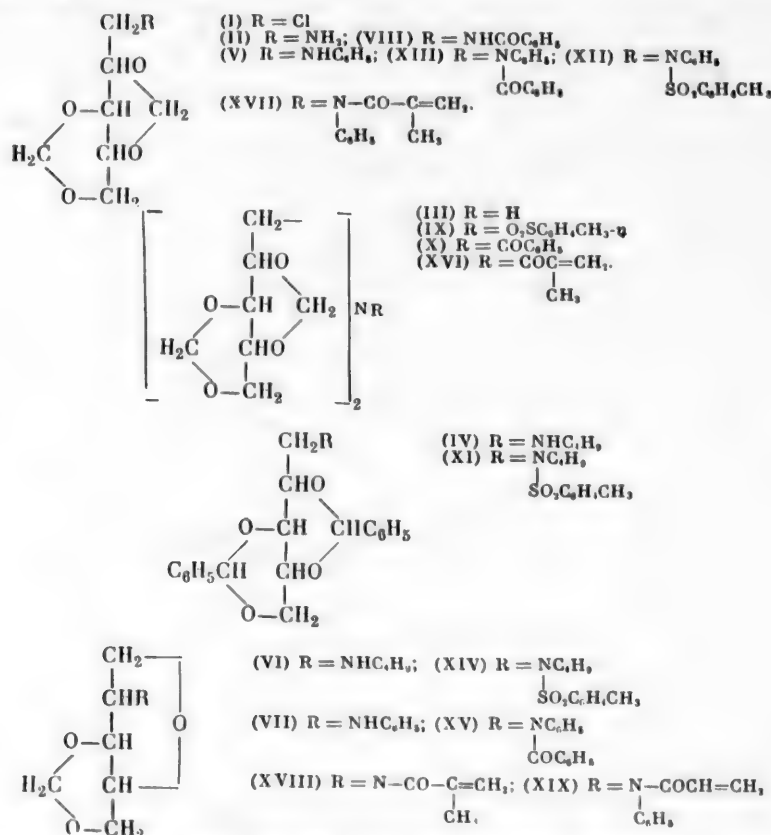
pp. 3544-3550, November, 1961

Original article submitted December 30, 1960

Continuing our previous investigation [1] on derivatives of xylitol and xylitan with the object of using them as monomers for polymerization, we have studied the amines and the methacrylamides based on them of acetals of xylitol and its monoanhydride.

Amination was carried out by replacing the tosyl groups in the tosylated acetal of xylitol 2,4:3,5-dimethylenexylitol and the tosyl ester of 3,5-methylene-1,4-xylitan, and by substitution of the chlorine in the chlorohydrin of 2,4:3,5-dimethylenexylitol.

On replacing the tosyl group in 1-tosyl-2,4:3,5-dimethylenexylitol by an ammonia residue, a secondary amine was obtained, while in the analogous reaction with 1-chloro-1-deoxy-2,4:3,5-dimethylenexylitol, a mixture of secondary and primary amines of dimethylenexylitol was obtained.



\*Eighth communication of the series: Anhydrides and amino and guanido. derivatives of carbohydrates and polyhydric alcohols; 7th communication of the series, see *ZhOKh*, 28, 3238 (1958).

We have reported the following for the first time: 1-Chloro-1-deoxy-2,4:3,5-dimethylenexylitol (I); 1-amino-2,4:3,5-dimethylenexylitol (II) and the benzoylamino-2,4:3,5-dimethylenexylitol (VIII) from it; 1-amino-bis-(2,4:3,5-dimethylenexylitol) (III), and the *p*-toluenesulfonamido-bis-(2,4:3,5-dimethylenexylitol) (IX) and benzamido-bis-(2,4:3,5-dimethylenexylitol) (X) obtained from it; 1-butylamino-2,4:3,5-dibenzylidenexylitol (VI), and the 1-butyl-*p*-toluenesulfonamido-2,4:3,5-dibenzylidenexylitol (XI) obtained from it; 1-phenylamino-2,4:3,5-dimethylenexylitol (V), and the 1-*N*-phenyl-*p*-toluenesulfonamido-2,4:3,5-dimethylenexylitol (XII) and the phenylbenzamido-2,4:3,5-dimethylenexylitol (XIII) obtained from it; 2-butylamino-3,5-methylene-1,4-xylitan (VI) and the 2-*N*-butyl-*p*-toluenesulfonamido-3,5-methylene-1,4-xylitan (XIV) obtained from it; and 2-phenylamino-3,5-methylene-1,4-xylitan (VII) and the 2-phenylbenzamido-3,5-methylene-1,4-xylitan (XV) synthesized from it.

The action of methacrylic and acrylic acid chlorides on (III), (V), and (VII), yielded: 1-Methacrylamido-bis-(2,4:3,5-dimethylenexylitol) (XVI); 1-*N*-phenylmethacrylamido-2,4:3,5-dimethylenexylitol (XVII); 2-*N*-phenylmethacrylamido-3,5-methylene-1,4-xylitan (XVIII); and 2-*N*-phenylacrylamido-3,5-methylene-1,4-xylitan (XIX).

The properties of the compounds and the conditions of their synthesis are reported in the experimental part.

#### EXPERIMENTAL PART

The tosyl esters of 2,4:3,5-dimethylenexylitol, 2,4:3,5-dibenzylidenexylitol, and 3,5-methylene-1,4-xylitan were obtained according to direction in the literature [2-4].

The tosyl ester of 2,4:3,5-dimethylenexylitol had m.p. 146° (literature data 146° [2]), the tosyl ester of 2,4:3,5-dibenzylidenexylitol had m.p. 146° (literature data 146.147° [5]), and the tosyl ester of 3,5-methylene-1,4-xylitan had m.p. 85°, which agrees with literature data [4].

**1-Chloro-1-deoxy-2,4:3,5-dimethylenexylitol (I).** To a solution of 20 g of the dimethylenexylitol in 80 ml of dry pyridine, being stirred in a three-necked flask with a stirrer, reflux condenser, and dropping funnel, 40 ml of thionyl chloride was added, the reaction mixture being cooled to 0°. After the completion of the addition, the reaction mixture was stirred for 1 hour 30 minutes at 0° and 1 hour 30 minutes at 100°. The cooled solution was poured into ice water. After the addition of 50 ml of chloroform to the aqueous solution, the oily layer was separated, washed with cold 5% sodium bicarbonate solution, and with water to neutrality, and dried with sodium sulfate. The solvent was distilled off and the residue recrystallized from ethyl alcohol. A yield of 14 g of a substance with m.p. 129° was obtained. 1-Chloro-1-deoxy-2,4:3,5-dimethylenexylitol dissolves in the cold in many organic solvents and in water. It dissolves in ether on warming.

Found %: C 43.14; H 5.76; Cl 18.06.  $C_7H_{11}O_4Cl$ . Calculated %: C 43.18; H 5.65; Cl 18.24.

**Amino-bis-(2,4:3,5-dimethylenexylitol) (III).** A solution of 15 g of the tosyl ester of 2,4:3,5-dimethylenexylitol in 50 ml of methyl alcohol saturated at 0° with ammonia was heated in an autoclave to 125° for 36 hours. The cooled reaction mixture consisted of a crystalline precipitate of amino-bis-(2,4:3,5-dimethylenexylitol) and a pale yellow solution containing *p*-toluenesulfonic acid salts of amines and salts of quaternary ammonium bases. The crystalline amino-bis-(2,4:3,5-dimethylenexylitol) was purified by two recrystallizations from hot aqueous alcohol (50:50). A yield of 9.2 g (54%) of a substance in the form of a powder with m.p. 234-240° (decomp.) was obtained. This compound does not dissolve appreciably in ethyl alcohol and dioxan. It is slightly soluble in cold water and readily soluble in hot water. It does not dissolve in ether and chloroform.

Found %: C 50.71; H 7.18; N 4.35.  $C_{14}H_{23}O_8N$ . Calculated %: C 50.45; H 6.91; N 4.21.

The filtrate remaining after the removal of the crystalline amino-bis-(2,4:3,5-dimethylenexylitol) was evaporated to eliminate the ammonia. The dry residue was stirred with chloroform (10 ml) and added to a solution of sodium ethoxide in ethyl alcohol. The mixture was shaken in a machine for 3 hours, evaporated to dryness, and extracted with chloroform to remove the primary amine. After distillation of the solvent, amino-2,4:3,5-dimethylenexylitol was obtained in the form of a microcrystalline powder (0.15 g) with m.p. 120-121°. The amino-2,4:3,5-dimethylenexylitol was characterized in the form of its benzoyl derivative.

\*All the analyses in the present investigation were carried out by our colleagues of the analytical laboratory of the Institute of High Molecular Weight Compounds, for which the authors express their deep appreciation to them.

Benzamido-2,4:3,5-dimethylxylitol (VIII) was obtained from 0.1 g of (II) and 0.1 g of benzoyl chloride in 5 ml of pyridine at room temperature. After isolation by the usual method and recrystallization from ethyl alcohol, the substance was obtained in the form of needle-like crystals, soluble in the majority of organic solvents. M.p. 214-215°.

Found %: C 59.95; H 6.50; N 4.96.  $C_{14}H_{17}O_5N$ . Calculated %: C 60.22; H 6.09; N 5.02.

1-Amino-2,4:3,5-dimethylenexylitol (II) and 1-amino-bis(2,4:3,5-dimethylenexylitol) (III) from 1-chloro-1-deoxy-2,4:3,5-dimethylenexylitol (I). A mixture of 10 g of (I) and 50 ml of 90% aqueous methyl alcohol saturated with ammonia at 0° was heated in an autoclave for 72 hours at 180°. The crystalline 1-amino-bis(2,4:3,5-dimethylenexylitol) (III) was filtered off and purified by recrystallization, as described above. M.p. 234-240° (decomp.). A yield of 5.2 g (30%) of amorphous product in the form of a powder was obtained. A mixed sample with the amino-bis-(2,4:3,5-dimethylenexylitol) obtained in the preceding experiment showed no depression of the melting point. The filtrate, containing the primary amine and p-toluenesulfonic acid salts of amines, was evaporated until the ammonia had been completely removed. The residue (7.6 g) was dissolved in 40 ml of water and heated with stirring with 7 g of barium hydroxide for 3 hours at 60° and 10 minutes at the boil. The mixture was evaporated to dryness, and the residue was dried to constant weight in a vacuum desiccator and extracted with hot chloroform. After distilling off the solvent, 2.10 g (30%) of 1-amino-2,4:3,5-dimethylenexylitol (II) was obtained in the form of fine needles. M.p. 120-121°. It dissolves in the cold in the majority of organic solvents and in water.

Found %: C 47.99; H 7.41; N 7.62.  $C_7H_{13}O_4N$ . Calculated %: C 48.00; H 7.42; N 8.00.

p-Toluenesulfonamido-bis-(2,4:3,5-dimethylenexylitol) (IX) was obtained from 0.5 g of (III) by the action of p-toluenesulfonyl chloride in pyridine at room temperature. After freeing it from pyridine, it had m.p. 211-212° (from alcohol). p-Toluenesulfonamido-bis-(2,4:3,5-dimethylenexylitol) dissolves in the hot in alcohol, chloroform, and pyridine, and does not dissolve in ether and water.

Found %: C 51.84; H 6.22; N 2.98; S 6.53.  $C_{21}H_{29}O_{16}NS$ . Calculated %: C 51.74; H 5.95; N 2.87; S 6.57.

Benzamido-bis-(2,4:3,5-dimethylenexylitol) (X) was obtained from 0.5 g of (III) and 0.3 g of benzoyl chloride in pyridine. After recrystallization from a large volume of boiling alcohol, it had m.p. 261-262°. The substance is soluble to a limited extent in alcohol and chloroform and does not dissolve in water.

Found %: C 57.77; H 5.26; N 3.26.  $C_{21}H_{27}O_9N$ . Calculated %: C 57.67; H 6.18; N 3.20.

1-Butylamino-2,4:3,5-dibenzylidenexylitol (IV) was obtained on heating 4.8 g of 1-tosyl-2,3:4,5-dibenzylidenexylitol with 25 ml of butylamine in a tube at 120° for 72 hours. After 12 hours' shaking of the solution, diluted with chloroform (20 ml), with sodium carbonate, and the removal of the sediment and the solvent, the residue was recrystallized from alcohol. The substance (2 g) was obtained in the form of a white amorphous powder with m.p. 146°, soluble in alcohol, benzene, and chloroform, but insoluble in water.

Found %: C 72.00; H 7.56; N 3.73.  $C_{23}H_{29}O_4N$ . Calculated %: C 72.06; H 7.57; N 3.65.

1-N-Butyl-p-toluenesulfonamido-2,4:3,5-dibenzylidenexylitol (XI) was obtained from 0.6 g of (IV) and 0.5 g of p-toluenesulfonyl chloride in 10 ml of pyridine. After isolation in the usual way, the substance was obtained in the form of fine needles with m.p. 126-127° (from alcohol).

Found %: C 66.75; H 6.83; N 2.63; S 5.82.  $C_{30}H_{35}O_6NS$ . Calculated %: C 67.04; H 6.51; N 2.60; S 5.95.

1-Phenylamino-2,4:3,5-dimethylenexylitol (V). A mixture of 20 g of 1-tosyl-2,4:3,5-dimethylenexylitol and 50 g of aniline was heated in a tube at 100° for 130 hours. After cooling the tube, the solution was diluted with 50 ml of dry chloroform and shaken with sodium carbonate for 12 hours. The sediment was filtered off and the solution evaporated in vacuum. The residue was recrystallized from alcohol. A yield of 12 g (78%) of the substance in the form of a white amorphous powder was obtained; m.p. 133°; it dissolves on heating in alcohols, chloroform, and acetone, and does not dissolve in water.

Found %: C 62.20; H 7.12; N 5.68.  $C_{13}H_{17}O_4N$ . Calculated %: C 62.15; H 6.77; N 5.58.

1-N-Phenyl-p-toluenesulfonamido-2,4:3,5-dimethylenexylitol (XII) was obtained by the reaction of 1-phenylamino-2,4:3,5-dimethylenexylitol (V) with p-toluenesulfonylchloride in pyridine during 24 hours. The substance was obtained in the form of fine needles with m.p. 176° (from alcohol); it dissolves in the hot in alcohols, chloroform, and acetone.

Found %: C 59.40; H 5.68; N 3.48; S 7.52.  $C_{20}H_{23}O_6NS$ . Calculated %: C 59.26; H 5.68; N 3.46; S 7.90.

1-N-Phenylbenzamido-2,4:3,5-dimethylenexylitol (XIII) was obtained from (V) by the action of benzoyl chloride in pyridine in the form of needle-like crystals. M.p. 178° (from ethyl alcohol). It dissolves on heating in alcohol, benzene, and chlorinated hydrocarbons.

Found %: C 67.80; H 6.50; N 3.93.  $C_{20}H_{21}O_5N$ . Calculated %: C 67.60; H 5.92; N 3.94.

2-Butylamino-3,5-methylene-1,4-xylitan\* (VI) was obtained by heating 12.0 g of tosyl ester of 3,5-methylene-1,4-xylitan with 10 ml of butylamine for 92 hours at 120°. After dilution with 20 volumes of dry ether, the removal of salts and of the solvent, the syrupy residue was distilled in vacuum. The main fraction distilled between 80 and 85° (0.4 mm). The colorless oily liquid crystallized immediately. The substance was washed on the filter with 3 portions of cold n-hexane. Colorless crystals in the form of plates were obtained with m.p. 34-35°, soluble in the cold in the majority of organic solvents and in water.

Found C 60.15; H 9.52; N 7.50.  $C_{10}H_{19}O_3N$ . Calculated %: C 59.70; H 9.44; N 7.00.

2-N-Butyl-p-toluenesulfonamido-3,5-methylene-1,4-xylitan (XIV) was synthesized from 0.5 g of (VI) and 0.55 g of p-toluenesulfonyl chloride in 10 ml of pyridine. After isolation by the usual method, 0.42 g of a substance with m.p. 110° (from alcohol) was obtained in the form of microcrystals, soluble in alcohol, benzene, and acetone.

Found %: C 57.22; H 7.23; N 4.07; S 8.98.  $C_{17}H_{25}O_5NS$ . Calculated %: C 57.47; H 7.04; N 3.94; S 9.01.

2-Phenylamino-3,5-methylene-1,4-xylitan (VII). A mixture of 0.15 g of the tosyl ester of 3,5-methylene-1,4-xylitan and 48 g of aniline was heated in a tube for 72 hours at 140°. After eliminating the salts by diluting the reaction mixture with 70 ml of ether, and distilling the latter, the residue was recrystallized twice from alcohol. A yield of 7.2 g of lemon yellow needles with m.p. 123-124° was obtained, soluble in alcohol, chloroform, benzene, and acetone, and insoluble in water.

Found %: C 65.40; H 7.00; N 6.52.  $C_{12}H_{15}O_3N$ . Calculated %: C 65.15; H 6.83; N 6.33.

2-N-Phenylbenzamido-3,5-methylene-1,4-xylitan (XV) was obtained from 0.5 g of (VII) and 0.4 g of benzoyl chloride in 7 ml of pyridine. After isolation in the usual way, the phenylbenzamido-3,5-methylene-1,4-xylitan was obtained in the form of fine crystals with m.p. 128° (from alcohol) soluble in hot alcohol, benzene and chloroform.

Found %: C 69.65; H 5.91; N 4.22.  $C_{18}H_{19}O_4N$ . Calculated %: C 70.15; H 5.85; N 4.30.

Methacrylamido-bis-(2,4:3,5-dimethylenexylitol) (XVI). A mixture of 0.025 mole of amino-bis-(2,4:3,5-dimethylenexylitol), 20 ml of dry chloroform, and 0.026 mole of dimethylaniline was placed in a three-necked flask with a stirrer, a reflux condenser, and a dropping funnel. From the dropping funnel, 0.025 mole of methacrylic acid chloride was added slowly. After the addition of the acid chloride, the reaction mixture was stirred for a further 2 hours and left overnight. On the next day, 25 ml of chloroform was added and the solution was washed successively with 3% hydrochloric acid, 5% sodium carbonate, and water. After distilling off the solvent, the residue was recrystallized from ethyl alcohol. The microcrystalline white powder with m.p. 217° dissolved on heating in the majority of organic solvents, but not in water. Yield 30%.

Found %: C 53.90; H 7.05; N 3.71.  $C_{18}H_{27}O_9N$ . Calculated %: C 53.84; H 6.74; N 3.49.

1-N-Phenylmethacrylamido-2,4:3,5-dimethylenexylitol (XVII) was obtained similarly from 0.025 mole of 1-phenylamino-2,4:3,5-dimethylenexylitol and 0.025 mole of methacrylic acid chloride in the presence of 0.026 mole of dimethylamine and 25 ml of chloroform. Amorphous white powder with m.p. 193° (from alcohol). Yield 75%. The substance dissolves in alcohols, benzene, chloroform, and dioxane, but does not dissolve in water.

Found %: C 64.25; H 7.00; N 4.49.  $C_{17}H_{21}O_5N$ . Calculated %: C 63.95; H 6.58; N 4.39.

2-N-Phenylmethacrylamido-3,5-methylene-1,4-xylitan (XVIII) was obtained from 0.025 mole of 2-phenylamino-3,5-methylenexylitan (V) and 0.025 mole of methacrylic acid chloride in the presence of 0.026 mole of dimethylaniline in dichloroethane (40 ml). Lemon-colored needle-like crystals with m.p. 114° (from alcohol). Yield 43%. The substance dissolves on heating in alcohols, benzene, chloroform, and dichloroethane, but does not dissolve in water.

\* With the participation of Yu. I. Dmitriev.

Found %: C 66.20; H 6.96; N 4.82.  $C_{16}H_{19}O_4N$ . Calculated %: C 66.43; H 6.59; N 4.84.

2-N-Phenylacrylamido-3,5-methylene-1,4-xylitan (XIX) was obtained from 0.025 mole of 2-phenylamino-3,5-methylene-1,4-xylitan and 0.026 mole of acrylic acid chloride in the presence of 0.027 mole of dimethylaniline and 30 ml of chloroform. A rise in temperature of the reaction mixture was observed on the addition of the acrylic acid chloride; therefore the flask was periodically cooled in cold water. Pale yellow crystals with m.p. 103° (from alcohol). The substance dissolves in alcohol, benzene, chloroform, and dichloroethane. It does not dissolve in water.

Found %: C 65.34; H 5.98; N 5.44.  $C_{15}H_{17}O_4N$ . Calculated %: C 65.45; H 6.18; N 5.00.

#### SUMMARY

1. The reaction of the tosyl esters of 2,4:3,5-dimethylenexylitol, 2,4:3,5-dibenzylidenexylitol, and 3,5-methylene-1,4-xylitan with ammonia, butylamine and aniline, and the reaction of 1-chloro-1-deoxy-2,4:3,5-dimethylenexylitol with ammonia have been studied. New amino derivatives of the above acetals of xylitol and xylitan have been obtained.

2. The benzoyl-, p-toluenesulfonyl-, acryloyl-, and methacryloylamino derivatives have been synthesized.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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REACTION OF CARBON TETRACHLORIDE WITH ALKYL  
ESTERS OF p-CHLOROPHENYL-, p-ISOPROPYLPHENYL-,  
AND  $\alpha$ -NAPHTHYLPHOSPHINOUS ACIDS

Gil'm Kamai, F. M. Kharrasova, R. B. Sultanova,  
and S. Yu. Tukhvatullina

S. M. Kirov Kazan Chemical-technological Institute  
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It was previously shown that phosphinous acid esters readily undergo reaction with carbon tetrachloride to form trichloromethylphosphinic derivatives with the elimination of alkyl chlorides [1].

As continuation and development of our studies we investigated the reaction between alkyl p-chlorophenyl-, p-isopropylphenyl-, and  $\alpha$ -naphthylphosphinites and carbon tetrachloride.

Starting p-chlorophenyl- and p-isopropylphenyldichlorophosphines were prepared from phosphorous trichloride and chlorobenzene, and similarly, isopropylbenzene, in the presence of aluminum chloride by decomposition of the initial phosphorous oxychloride [2, 3] complex. The yield of p-chlorophenyldichlorophosphine was 60%, while that of p-isopropylphenyldichlorophosphine was 25%.  $\alpha$ -Naphthyldichlorophosphine was accessible with difficulty. Synthesis of its mercury [4] or zinc [5] derivative was of little use. The Friedel-Crafts [2] reaction was unsuccessful for preparing it, since the initially-formed complex of naphthalene, phosphorous trichloride, and aluminum chloride was so stable that it could not be decomposed by water [6], phosphorous oxychloride [3], or pyridine [7].

$\alpha$ -Naphthyldichlorophosphine was obtained by a literature procedure [8, 9] via an organocadmium derivative of naphthalene, prepared by treating the Grignard reagent with cadmium chloride. The yield of  $\alpha$ -naphthyldichlorophosphine was 15-20%.

p-Chlorophenyl-, p-isopropylphenyl-, and  $\alpha$ -naphthylphosphinite esters, with the exception of the latter methyl ester, had not been described in the literature. We synthesized them by reacting the corresponding aryldichlorophosphine with alcohol in the presence of pyridine or triethylamine (B).



Some properties of the esters obtained are given in Table 1.

As is apparent from the data in Table 1, the foregoing arylphosphinites were obtained in 50-80% yields. We were unable to isolate only allyl  $\alpha$ -naphthylphosphinite. Its isomerization product was isolated during attempts to prepare this ester. A large portion of the ester remained as undistillable tars.

The reaction between the esters obtained and carbon tetrachloride occurred readily. The first representatives reacted even at room temperature. But in each discrete case 4-6 hr heating with a reflux condenser was needed for complete reaction. The reaction occurred according to the general scheme



with formation of the corresponding aryltrichloromethylphosphinate. Some properties of the esters obtained are given in Table 2.

The low yields (30-70%), apparently, are explained by possible secondary reactions of a radical-chain character [1] as well as by thermal instability of aryltrichloromethylphosphinates. Although the methyl and ethyl esters can

TABLE 1

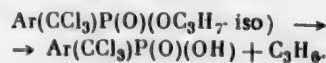
Formula for compound	Boiling point (pressure in mm)	$n_D^{20}$	$d_4^{20}$	Empirical formula	% P		Yield (in %)
					found	calc.	
1. $\text{P-ClC}_6\text{H}_4\text{P}(\text{OC}_2\text{H}_5)_2$	129—130.5° (11)	1.5252	1.1210	$\text{C}_{10}\text{H}_{14}\text{O}_2\text{ClP}$	13.38	13.27	78.7
2. $\text{P-ClC}_6\text{H}_4\text{P}(\text{OC}_3\text{H}_7\text{-iso})_2$	138.5—139 (11)	1.5108	1.0880	$\text{C}_{12}\text{H}_{18}\text{O}_2\text{ClP}$	11.32	11.84	38.0
3. $\text{P-ClC}_6\text{H}_4\text{P}(\text{OC}_3\text{H}_7\text{-n})_2$	153 (12)	1.5179	1.0990	$\text{C}_{12}\text{H}_{18}\text{O}_2\text{ClP}$	11.85	11.89	56.0
4. $\text{P-ClC}_6\text{H}_4\text{P}(\text{OC}_4\text{H}_9\text{-n})_2$	172—173 (14)	1.5096	1.0700	$\text{C}_{14}\text{H}_{22}\text{O}_2\text{ClP}$	10.72	10.69	55.0
5. $\text{P-CH}_3\text{CH}(\text{CH}_3)\text{C}_6\text{H}_4\text{P}(\text{OC}_2\text{H}_5)_2$	132—134 (11)	1.5055	0.9886	$\text{C}_{13}\text{H}_{21}\text{O}_2\text{P}$	13.12	12.89	53.7
6. $\text{P-CH}_3\text{CH}(\text{CH}_3)\text{C}_6\text{H}_4\text{P}(\text{OC}_3\text{H}_7\text{-n})_2$	163—165 (12)	1.5009	0.9802	$\text{C}_{15}\text{H}_{25}\text{O}_2\text{P}$	11.82	11.55	68.6
7. $\alpha\text{-C}_{10}\text{H}_7\text{P}(\text{OCH}_3)_2$ *	137—138 (4)	1.6096	1.1550	$\text{C}_{12}\text{H}_{13}\text{O}_2\text{P}$	14.12	14.07	45.2
8. $\alpha\text{-C}_{10}\text{H}_7\text{P}(\text{OC}_2\text{H}_5)_2$	167—168 (10)	1.5848	1.1000	$\text{C}_{14}\text{H}_{17}\text{O}_2\text{P}$	12.36	12.47	59.4
9. $\alpha\text{-C}_{10}\text{H}_7\text{P}(\text{OC}_3\text{H}_7\text{-iso})_2$	176—178 (12)	1.5648	1.0671	$\text{C}_{16}\text{H}_{21}\text{O}_2\text{P}$	10.56	11.21	47.6
10. $\alpha\text{-C}_{10}\text{H}_7\text{P}(\text{OC}_3\text{H}_7\text{-n})_2$	188—189.5 (12)	1.5672	1.0630	$\text{C}_{16}\text{H}_{21}\text{O}_2\text{P}$	11.11	11.21	67.0
11. $\alpha\text{-C}_{10}\text{H}_7\text{P}(\text{OC}_4\text{H}_9\text{-n})_2$	175—176 (4)	1.5575	1.0401	$\text{C}_{18}\text{H}_{25}\text{O}_2\text{P}$	10.40	10.2	50.0
12. $\alpha\text{-C}_{10}\text{H}_7\text{P}(\text{O})(\text{C}_3\text{H}_7)(\text{OC}_3\text{H}_7)$	179.5—180 (4)	1.5832 (or 50°)	1.1239 (or 50°)	$\text{C}_{16}\text{H}_{17}\text{O}_2\text{P}$	11.60	11.37	33.0

\* Literature data (81): B.p. 101° (0.15 mm),  $n_D^{20}$  1.6127.

TABLE 2

Formula for compound	Boiling point (pressure in mm)	n <sub>D</sub> <sup>20</sup>	d <sub>4</sub> <sup>20</sup>	Empirical formula	% P		Yield (in %)
					Found	Calc.	
1. $\text{p-ClC}_6\text{H}_4(\text{CCl}_3)_2\text{P}(\text{O})(\text{OC}_2\text{H}_5)$	155-156.5 (3)	1.5572	1.4590	$\text{C}_9\text{H}_9\text{O}_2\text{Cl}_4\text{P}$	9.58	9.63	59.0
2. $\text{p-ClC}_6\text{H}_4(\text{CCl}_3)_2\text{P}(\text{O})(\text{OC}_3\text{H}_7\text{-n})$	158.8-159.3 (1.5-2)	1.5378	1.3530	$\text{C}_{10}\text{H}_{11}\text{O}_2\text{Cl}_4\text{P}$	9.57, 9.48	9.22	54.0
3. $\text{p-ClC}_6\text{H}_4(\text{CCl}_3)_2\text{P}(\text{O})(\text{OC}_4\text{H}_9\text{-n})$	153.5 (1.5-2)	1.5390	1.3290	$\text{C}_{11}\text{H}_{13}\text{O}_2\text{Cl}_4\text{P}$	8.96, 8.46	8.81	45.0
4. $\text{p-CH}_3\text{CH}_2\text{CH}_2\text{CH}_2(\text{CCl}_3)_2\text{P}(\text{O})(\text{OC}_2\text{H}_5)$	145.5-147 (2)	1.5350	1.2740	$\text{C}_{12}\text{H}_{16}\text{O}_2\text{Cl}_3\text{P}$	9.55, 9.73	9.68	52.2
5. $\text{p-CH}_3\text{CH}_2\text{CH}_2\text{CH}_2(\text{CCl}_3)_2\text{P}(\text{O})(\text{OC}_3\text{H}_7\text{-n})$	170 (3)	1.5127	1.1550	$\text{C}_{13}\text{H}_{18}\text{O}_2\text{Cl}_3\text{P}$	9.60, 9.90	9.02	30.0
6. $\alpha\text{-C}_{10}\text{H}_7(\text{CCl}_3)_2\text{P}(\text{O})(\text{OCH}_3)$	205-207 (5) T. M. P. 101.5-102° 179-180 (3) T. M. P. 80-80.5°	—	—	$\text{C}_{12}\text{H}_{10}\text{O}_2\text{Cl}_3\text{P}$	9.51, 9.90	9.55	42.5
7. $\alpha\text{-C}_{10}\text{H}_7(\text{CCl}_3)_2\text{P}(\text{O})(\text{OC}_2\text{H}_5)$	230 (4) decomp. 186-187 (1)	—	—	$\text{C}_{13}\text{H}_{12}\text{O}_2\text{Cl}_3\text{P}$	9.24, 9.08	9.18	61.8
8. $\alpha\text{-C}_{10}\text{H}_7(\text{CCl}_3)_2\text{P}(\text{O})(\text{OC}_3\text{H}_7\text{-iso})$	300 decomposed in bath (5)	1.4930	1.3300	$\text{C}_{14}\text{H}_{14}\text{O}_2\text{Cl}_3\text{P}$	8.25, 8.45	8.81	74.6
9. $\alpha\text{-C}_{10}\text{H}_7(\text{CCl}_3)_2\text{P}(\text{O})(\text{OC}_3\text{H}_7\text{-n})$		1.5991	1.3460	$\text{C}_{14}\text{H}_{14}\text{O}_2\text{Cl}_3\text{P}$	8.65	8.81	73.2
10. $\alpha\text{-C}_{10}\text{H}_7(\text{CCl}_3)_2\text{P}(\text{O})(\text{OC}_4\text{H}_9\text{-n})$		1.5895	—	$\text{C}_{15}\text{H}_{16}\text{O}_2\text{Cl}_3\text{P}$	8.86, 8.23	8.47	92.0

still be purified by distillation under a pressure of 1-5 mm, the isopropyl and butyl esters were vigorously decomposed during attempted distillation. The decomposition, apparently, occurs with elimination of the corresponding aryltrichloromethylphosphinic acid.



This supposition is confirmed by the fact that isopropyl p-chlorophenyl- and  $\alpha$ -naphthyltrichloromethylphosphinates are decomposed by attempted vacuum distillation. Free p-chlorophenyltrichloromethyl- and, correspondingly,  $\alpha$ -naphthyltrichloromethylphosphinic acids were isolated from the decomposition products.

#### EXPERIMENTAL PART

Ethyl  $\alpha$ -Naphthylphosphinite (Table 1, No. 9). In a three-necked flask equipped with a reflux condenser, stirrer, dropping funnel, thermometer, and feed for gaseous carbon dioxide, was charged a mixture of 12.8 g of absolute alcohol and 22 g of dry pyridine in 250 ml of absolute ether. The mixture was cooled in an ice-salt bath. A solution of 31.8 g of  $\alpha$ -naphthyltrichloromethylphosphine in 100 ml of ether was slowly added from the dropping funnel in a stream of carbon dioxide. The temperature was maintained at  $-5^\circ$  to  $+5^\circ$  during this. After 0.5 hr of stirring at room temperature and 0.5 more at mild reflux of ether the reaction mixture was again carefully cooled with an ice-salt mixture. Pyridine hydrochloride was filtered, the residue was washed with ether (4 times with 25 ml). The filtrate was concentrated and distilled under vacuum. After 2 subsequent distillations from an Arbuzov flask 20.3 g of ethyl  $\alpha$ -naphthylphosphinite was obtained.

The other esters tabulated in Table 1 were obtained in an analogous manner.

Methyl  $\alpha$ -naphthylphosphinite (Table 1, No. 8) was obtained in the presence of triethylamine.

Ethyl  $\alpha$ -Naphthyltrichloromethylphosphinate (Table 2, No. 7) was obtained by the reaction of ethyl  $\alpha$ -naphthylphosphinite with carbon tetrachloride. In a flask, equipped with reflux condenser and feed for gaseous carbon dioxide, was charged a mixture of 10 g of ethyl  $\alpha$ -naphthylphosphinite and 20 ml of carbon tetrachloride. An energetic reaction with boiling of the mixture set in after several minutes. At the conclusion of the spontaneous reaction the reaction mixture was boiled for 4 hr. Then excess carbon tetrachloride was distilled off; the residue was distilled under vacuum. A thick mass (8.4 g) which crystallized upon grinding, and which was recrystallized from 72% aqueous alcohol (1:85) was obtained.

The remaining aryltrichloromethylphosphinates given in Table 2 were obtained similarly.

$\alpha$ -Naphthyltrichloromethylphosphinic Acid was isolated from the product of the reaction between isopropyl  $\alpha$ -naphthylphosphinite and carbon tetrachloride. A mixture of 7 g of isopropyl  $\alpha$ -naphthylphosphinite and 20 ml of carbon tetrachloride was heated under reflux for 4 hr in a stream of gaseous carbon dioxide. Then the excess carbon tetrachloride was distilled off. Upon attempted distillation the residue began to decompose vigorously at a bath temperature above 230° and a pressure of 4 mm. The remaining resinous product (8.75 g) was dissolved in ether. The crystals which separated were pressed out and dried. M.p. 217-218° (from n-octane). The yield of gray powder was 2.25 g (29%).

Found %: P 9.91, 9.77. Equiv. 305.8.  $C_{11}H_9O_2Cl_3P$ . Calculated %: P 10.00. Equiv. 309.5.

p-Chlorophenyltrichloromethylphosphinic acid was isolated similarly in the form of colorless needles (from 3% hydrochloric acid), m.p. 198-199°.

Found %: P 10.25; 10.17.  $C_7H_5O_2Cl_3P$ . Calculated %: P 10.37.

#### SUMMARY

1. A series of alkyl p-chlorophenyl-, p-isopropylphenyl-, and  $\alpha$ -naphthylphosphinites were synthesized and studied.

2. It was found that the reaction between these esters and carbon tetrachloride took place with formation of alkyl aryltrichloromethylphosphinates.

3. It was shown that aryltrichloromethylphosphinates are thermally unstable; upon heating they partially decompose with elimination of olefins and a free aryltrichloromethylphosphinic acid.

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## SOME ESTERS OF PHENYLTHIOARSINOUS ACIDS

Gil'm Kamai and N. A. Chadaeva

Kazan Branch Chemical Institute,

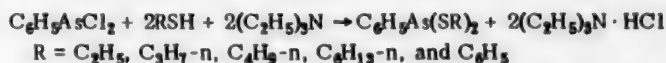
Academy of Sciences, USSR

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As a development of our studies in the area of thioesters of arsenic acids [1] we set a goal of studying the syntheses and properties of some esters of phenylthioarsinous acid. As a result of the experiments conducted it was shown that alkyl and aryl phenylthioarsinites are obtained by reaction of phenyldichloroarsine with the corresponding mercaptan in absolute ether in the presence of triethylamine according to the equation:



The constants and analytical data for the thioesters we obtained are given in the table.

The thioesters isolated, with the exception of phenyl phenylthioarsinite, are oils possessing an unpleasant odor and colored slightly yellow. They are readily soluble in common organic solvents and are slowly hydrolyzed by water, giving phenylarsine oxide and the corresponding mercaptan. The mean atomic refraction of arsenic in these thioesters is equal to 11.43.

The alkyl phenylthioarsinites synthesized were tested for physiological activity.\* It was established that they possessed insecticidal activity with reference to flour weevils and houseflies. With reference to warm-blooded animals these esters were more toxic than the alkyl ethylthioarsinites we synthesized earlier [1]. Thus, for subcutaneous introduction into white mice the lethal dose ( $\text{LD}_{100}$ ) for  $\text{n-C}_4\text{H}_9\text{S})_2\text{AsC}_6\text{H}_5$  was equal to 30 mg/kg, but for  $(\text{n-C}_4\text{H}_9\text{S})_2\text{AsC}_6\text{H}_5$  it was 7.5 mg/kg.

### EXPERIMENTAL PART

**Ethyl Phenylthioarsinite.** In a round-bottomed flask equipped with mechanical stirrer, reflux condenser, dropping funnel, and inlet tube for nitrogen was charged 17.0 g of ethyl mercaptan, 27.7 g of triethylamine, and 350 ml of absolute ether. The mixture was cooled to  $0^\circ$  and stirred during the dropwise addition of 30.49 g of phenyldichloroarsine. After the addition of the indicated amount of phenyldichloroarsine the mixture was heated to boiling and stirred for 1 hr. Upon cooling, the residue was filtered through a glass filter, and washed twice with dry ether. The liquid remaining after distillation of the solvent was distilled under vacuum from a Favorskii flask. The following were isolated: First: B.p.  $102\text{--}114^\circ$  (1-1.5 mm), weight 8.3 g; second: B.p.  $114\text{--}118^\circ$  (1 mm); weight 21.1 g; residue in flask was about 1 g.

After an additional distillation 15.1 g of ethyl phenylthioarsinite, the physical constants of which are given in the table (compound 1) was isolated from the second fraction. This ester is an oily liquid, slightly yellow, and had an unpleasant odor.

The remaining alkyl phenylthioarsinites were prepared in an analogous manner.

**Phenyl Phenylthioarsinite.** From 23.6 g of thiophenol, 21.67 g of triethylamine dissolved in 350 ml of absolute ether, and 23.8 g of phenyldichloroarsine, by a synthesis analogous to that of ethyl phenylthioarsinite 42 g of material was obtained after removal of triethylamine hydrochloride and distillation of the solvent.

\* Tests for physiological activity were conducted in the toxicological laboratory of the Kazan Branch Chemical Institute, Academy of Sciences, USSR under the direction of I. D. Neklesova.

No.	R	Boiling point (pressure in mm)	$d_4^{20}$	$n_D^{20}$	$M R_D$	$AR_{As}^R$	Empirical formula	% As		% S		Yield (in %)
								Found	Calc.	Found	Calc.	
1	$C_2H_5$ •	141—143 (2)	1.3071	1.6341	75.05	11.05	$C_{10}H_{15}S_2As$	26.79, 26.89	27.30	23.56, 23.75	23.41	40.34
2	$C_3H_7$ -n. ••	160—162 (2)	1.2396	1.6097	84.58	11.55	$C_{12}H_{19}S_2As$	24.56, 24.70	24.77	21.11, 21.32	21.21	57.17
3	$C_4H_9$ -n. •••	180—182 (2)	1.1881	1.5922	94.12	11.64	$C_{14}H_{23}S_2As$	22.46, 22.17	22.67	19.72, 19.85	19.41	57.66
4	$C_6H_{13}$ -n.	196—198 (1.5)	1.1366	1.5722	112.41	11.47	$C_{18}H_{31}S_2As$	18.91	19.38	16.28	16.59	10.25
5	$C_6H_5$	232—235 (2) M.P. 56-570	—	—	—	—	$C_{18}H_{15}S_2As$	20.38, 20.29	20.22	17.85	17.32	64.20

• Insecticidal activity: By spraying an 0.05% aqueous emulsion of this thioester 19% weevils died in 5 days and 19% of the houseflies within one day.

•• Insecticidal activity: By spraying an 0.08% aqueous emulsion 70.0% of the flour weevils died in 5 days, but at a thioester concentration of 0.1% 100% of the flour weevils died within one day.

••• Insecticidal activity: By spraying an 0.07% emulsion 65.0% of the flour weevils died within 5 days.

The phenyl phenylthioarsinite isolated was a crystalline substance with an unpleasant odor, colored slightly yellow. It was slowly decomposed by water, evolving thiophenol and phenylarsin oxide. The ester was readily soluble on heating in benzene, butyl acetate, ether, or gasoline but slightly soluble in absolute alcohol (Table, compound 5).

**Hydrolysis of Phenyl Phenylthioarsinite.** Phenyl phenylthiothioarsinite (3.5 g) was mixed with 50 ml of water. Then the mixture was heated for 2 hr on a boiling-water bath and allowed to stand for several days at room temperature. The white solid was filtered off, washed with water, and dried to constant weight. M.p. 123-125°, which corresponds to phenylarsine oxide.

## SUMMARY

Ethyl, n-propyl, n-butyl, n-hexyl, and phenyl phenylthioarsinites were prepared for the first time; some of their chemical and physical properties were studied.

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# STUDIES OF GLYCOL ETHERS AND THEIR DERIVATIVES

## XXXVI. SYNTHESIS AND CHEMICAL REACTIONS OF METHYLENE

### GLYCOL ETHERS

Shamkhal Mamedov and M. A. Avanesyan

Institute for Petrochemical Processes, Academy of Sciences,  
Azerbaijani SSR

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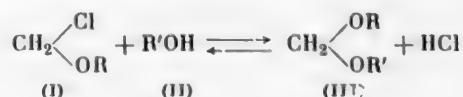
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Original article submitted October 3, 1959

One of us [1] showed previously that both symmetrical and asymmetrical methylene glycol ethers can be synthesized by reaction of  $\alpha$ -haloethers with mono- and polyhydric alcohols.

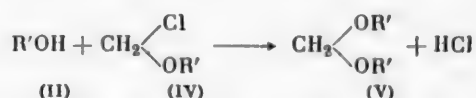
The purpose of the present work was extension of our initial work in the area of synthesizing glycol ethers [1].

The reaction of  $\alpha$ -haloethers with alcohols has, apparently, an equilibrium character, and the role of caustic under conditions of the "caustic" method is neutralization of the hydrogen halide evolved.



The possible formation of methylene glycol ethers (III) by direct reaction of  $\alpha$ -chloroethers with alcohols was confirmed by the observations of several investigators [2]. The formation of  $\alpha$ -chloroethers by the reaction of HCl with methylene glycol ethers in the cold, a reaction described in the literature [3], shows this. We established that HCl brought about preferential elimination of the alkoxy group of lesser weight. The yields of symmetrical methylene glycol ethers under conditions of the "caustic" method were high (80-90%) and side products were not formed [1], but during synthesis of asymmetric methylene glycol ethers the symmetric ethers were also formed (25-40%).

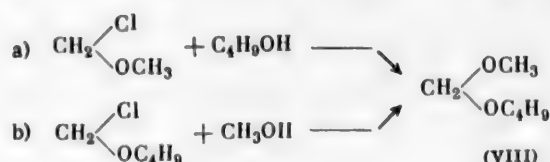
The formation of symmetric ethers as side products of reaction during synthesis of asymmetric [ethers] occurs only when the alkoxy group in the  $\alpha$ -haloether is of lesser weight than that in the alcohol used for synthesizing the asymmetric ether. In the reverse case, formation of the symmetric ether as a side product is not observed. Calcium oxide, in many cases, is substituted for solid NaOH; when dimethylaniline, pyridine, alcoholates, and 50% aqueous NaOH solution, in contrast, are used symmetrization does not occur. The formation of symmetric ethers occurs, apparently, owing to incomplete neutralization of hydrogen chloride formed during the reaction between the  $\alpha$ -chloroether and the alcohol. Excess hydrogen chloride, obviously, partially cleaves the reaction products with formation of  $\alpha$ -chloroether (I) and alcohol (II) or a new  $\alpha$ -chloroether (IV). In the latter case the new  $\alpha$ -chloroether (IV) can react with the starting alcohol (II) to form symmetric ether (V).



Dimethylaniline, alcoholic alcoholate solution, and 50% aqueous caustic, are mixed well with the reaction components and, obviously, allow for rapid and complete neutralization of the HCl. In cases when the alkoxy group in the  $\alpha$ -chloroether has a higher weight than in the alcohol taken for synthesis symmetrization does not occur since the HCl preferentially cleaves the alkoxy group of lesser weight with formation of the initial  $\alpha$ -chloroether. The latter, upon further reaction with the initial alcohol, again gives asymmetric ether, which almost excludes the possibility of forming symmetric ether.

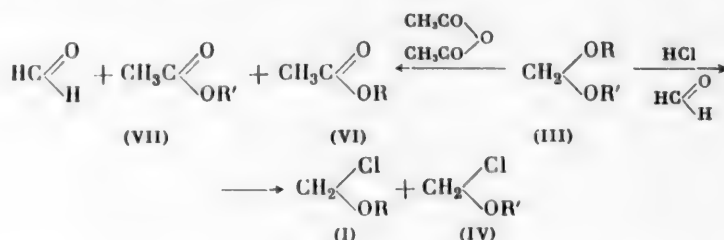
It was shown that dimethylaniline does not take part in the condensation reaction with  $\alpha$ -chloroethers [1] under the conditions of the "caustic" synthetic method. Dimethylaniline has some advantages over pyridine which it displaces, since it does not have a bad odor and is much more easily dried.

Frequently the boiling point of the ethers synthesized is very near that of the starting alcohol, which makes purification of the ether by distillation difficult. An excess of  $\alpha$ -chloroether (5-10%) completely removes this difficulty. However, during product work-up with water the excess  $\alpha$ -chloroether undergoes hydrolysis; it is possible in isolated cases to obtain alcohols the boiling point of which again is very near that of the ether. For example, the synthesis of ether (VIII) according to route "a" gives better results than according to scheme "b".



Work studying some chemical reactions of methylene glycol ethers was also carried out. It was shown that  $\text{PCl}_5$  reacts very energetically with methylene glycol ethers at ordinary temperatures with formation of an  $\alpha$ -chloroether (IV) and an alkyl halide.

Acetic anhydride almost does not react with common methylene glycol ethers under ordinary conditions; however, in the presence of traces of  $\text{H}_2\text{SO}_4$  the reaction begins with heat evolution (60-65°), and formaldehyde and acetate esters (VI and VII) are formed. A mixture of methylene glycol ether and trioxymethylene gives  $\alpha$ -chloroethers (I and IV) in good yields by reaction with  $\text{HCl}$ .



Symmetric methylene glycol ethers give only one form of  $\alpha$ -chloroether under the aforementioned conditions. On heating methylene glycol methylalkyl ethers with methanol in the presence of a small amount of  $\text{H}_2\text{SO}_4$  alcoholysis occurs with formation of methylene glycol dimethyl and the corresponding alcohol, which is a convenient method for establishing the structures of methylene glycol methylalkyl ethers. Methylene glycol ethers can be purified by distillation from metallic sodium.

#### EXPERIMENTAL PART

**Methyl n-Butyl Methylene Glycol Ether.** (VIII) a) To a mixture of 70 g of freshly-distilled dimethylaniline and 60 g of anhydrous ether was added 44 g of  $\alpha$ -chloromethyl ether with stirring. To the emulsion obtained 37 g of butyl alcohol was added dropwise at +20°; it was stirred 4 hr, and diluted with water. The ether extract was washed with 5%  $\text{H}_2\text{SO}_4$ , then with saturated  $\text{Na}_2\text{CO}_3$  solution. After drying and distillation of the solvent 28.7 g (48.6%) of ether (IX) was obtained by distillation; its constants are given in the table (compound 1).

b) To a mixture of 37 g of n-butyl alcohol and 24 g of powdered  $\text{NaOH}$  was gradually added 44 g of  $\alpha$ -chloromethyl ether with cooling (-12°) and stirring (1 hr), after which the mixture was diluted with water and the reaction product extracted with ether. After drying and distilling the solvent 8 g (13%) of ether (VIII) and 16 g (40%) of methylene glycol(dibutyl ether) [4] were separated by distillation.

c) Under experimental conditions (b) 25 g (69%) of ether (VIII) was obtained by reaction between 30.5 g of  $\alpha$ -chloromethylbutyl ether, and 10 g of methanol, and 12 g of powdered  $\text{NaOH}$ . Methylene glycol (dibutyl ether) was not obtained.

No.	R	R'	Yield (in %)	Boiling point (pressure in mm)	$n_D^{20}$	$d_4^{20}$	MR <sub>2</sub>		Found %		Empirical formula	Calculated %	
							Found	Calc.	C	H		C	H
1	CH <sub>3</sub>	n-C <sub>4</sub> H <sub>9</sub>	48.6	119-120° (760)	1.3880	0.8411	33.09	33.19	61.20	60.64	C <sub>6</sub> H <sub>14</sub> O <sub>2</sub>	61.01	11.72
2	CH <sub>3</sub>	tert.-C <sub>4</sub> H <sub>9</sub>	13	86-88 (760)	1.3844	0.8241	33.51	33.19	60.61	60.25	C <sub>6</sub> H <sub>14</sub> O <sub>2</sub>	61.01	11.72
3	CH <sub>3</sub>	n-C <sub>3</sub> H <sub>7</sub>	7.3	96-97 (760)	1.3796	0.8437	28.53	28.57	57.02	56.94	C <sub>5</sub> H <sub>12</sub> O <sub>2</sub>	57.69	11.54
4	CH <sub>3</sub>	iso-C <sub>5</sub> H <sub>11</sub>	62	136-137 (760)	1.3948	0.8428	37.82	37.80	63.98	63.83	C <sub>7</sub> H <sub>16</sub> O <sub>2</sub>	63.64	12.12
5	CH <sub>3</sub>	cyclo C <sub>6</sub> H <sub>11</sub>	55	59-60 (10)	1.4424	0.9474	40.21	40.23	66.64	66.71	C <sub>8</sub> H <sub>18</sub> O <sub>2</sub>	66.66	11.11
6	CH <sub>3</sub>	prim. n-C <sub>8</sub> H <sub>17</sub>	35	98-100 (14)	1.4160	0.8445	51.70	51.61	69.58	69.31	C <sub>10</sub> H <sub>22</sub> O <sub>2</sub>	69.96	12.65
7	C <sub>2</sub> H <sub>5</sub>	n-C <sub>4</sub> H <sub>9</sub>	40	136-137 (760)	1.3934	0.8387	37.58	37.80	63.32	63.40	C <sub>7</sub> H <sub>16</sub> O <sub>2</sub>	63.64	12.12
8	C <sub>2</sub> H <sub>5</sub>	cyclo C <sub>6</sub> H <sub>11</sub>	70	51-52 (15)	1.4372	0.9279	44.42	44.85	68.12	67.87	C <sub>9</sub> H <sub>18</sub> O <sub>2</sub>	68.35	11.39
9	n-C <sub>4</sub> H <sub>9</sub>	iso-C <sub>4</sub> H <sub>9</sub>	79	68-70 (10)	1.4030	0.8313	47.23	47.05	67.23	67.30	C <sub>9</sub> H <sub>20</sub> O <sub>2</sub>	67.50	12.50
10	n-C <sub>4</sub> H <sub>9</sub>	iso-C <sub>5</sub> H <sub>11</sub>	70	94-96 (10)	1.4150	0.8399	51.70	51.66	68.70	68.63	C <sub>10</sub> H <sub>22</sub> O <sub>2</sub>	68.96	12.65

d) To an emulsion formed 22 g of 50% aqueous NaOH and 16.7 g of n-butanol was added 20 g of  $\alpha$ -chloromethyl ether in an equal volume of ether with vigorous mixing and cooling (+18°) over 1 hr. After the usual work-up 9.5 g (36%) of ether (VIII), the constants of which agreed with those given in the preceding experiments, was isolated. Methylene glycol dibutyl ether was not formed.

e) To alcoholic caustic, prepared from 14 g of NaOH and 74 g of n-butyl alcohol was added 25 g of  $\alpha$ -chloromethyl ether. After the usual work-up 20 g (55%) of ether (VIII) was isolated. Methylene glycol dibutyl ether was not formed. Nine more new methylene glycol ethers, the constants for which are given in the table, were synthesized by methods (a) and (b).

Reaction of  $\text{PCl}_5$  with the Methyl n-Butyl Ether. (VIII). To 13 g of the ether in 40 ml of absolute ether, 28 g of  $\text{PCl}_5$  was added in portions with cooling. Then the flask was heated on a water bath (45-50°); a gas, which gave a luminous flame with a greenish border ( $\text{CH}_3\text{Cl}$ ), was evolved during this.  $\alpha$ -Chloromethyl butyl ether (2 g) boiling at 131-134°,  $d_4^{20}$  0.9434 was isolated from the residue by distillation.

Reaction of HCl with Methylene Glycol Methyl n-Butyl Ether (VIII). HCl was passed through a mixture consisting of 26 g of ether (IX) and 40 g of 50% aqueous  $\text{CaCl}_2$  solution until absorption stopped.  $\alpha$ -Chloromethyl butyl ether (5.5 g; 25%) boiling at 133-134°,  $d_4^{20}$  0.9143 was isolated by distillation from the upper layer after drying.

Reaction of Acetic Anhydride with (IX). To a mixture of 25 g of ether (IX) and 21 g of acetic anhydride was added 1.5 ml of conc.  $\text{H}_2\text{SO}_4$ . The mixture warmed up to 50-60°. It was stirred at this temperature for 2 hr. Butyl acetate (7 g; 29%), the constants of which corresponded to the literature data [5], was obtained.

Alcoholysis of Methylene Glycol Methyl Butyl Ether (IX). In a round-bottomed flask equipped with a fractionating column (height 50 cm) was charged 30 g of ether (VIII) and 150 g of methanol containing 3 ml of conc.  $\text{H}_2\text{SO}_4$ . The mixture was heated on a water bath (50°). Thus 18 g (93%) of methylene glycol dimethyl ether boiling at 42°;  $d_4^{20}$  0.8523;  $n_D^{20}$  1.3540 was distilled.

Literature data [6]: B.p. 42.5°;  $d_4^{18.2}$  0.8621;  $n_D^{20}$  1.3597.

n-Butyl alcohol (4 g) boiling at 116-117°;  $d_4^{20}$  0.8124;  $n_D^{20}$  1.3960 was isolated from the residue.

## SUMMARY

1. The reaction of  $\alpha$ -chloroethers with alcohols in the presence of various alkaline agents was studied.
2. Ten new methylene glycol ethers were synthesized.
3. Some chemical reactions of simple methylene glycol ethers were studied.

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# STUDIES OF GLYCOL ETHERS AND THEIR DERIVATIVES

## XXXVII. SYNTHESIS OF ALKYL $\beta$ -CHLOROETHYL AND ALKYL

### $\beta$ -ALKOXYETHYL ETHERS OF METHYLENE GLYCOL

Shamkhal Mamedov and A. S. Rzaev

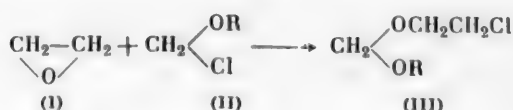
Institute for Petrochemical Processes, Academy of Sciences,  
Azerbaijan, SSR

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pp. 3561-3566, November, 1961

Original article submitted May 10, 1960

It was previously shown that simple  $\gamma$ -chloroethers exhibit insecticidal properties [1].

The goal of this work was synthesis and study of biologically active methylene glycol ethers with different functional atoms or groups in the  $\beta$ -position to the ether oxygen bridge, in particular methylene glycol alkyl  $\beta$ -chloroethyl ethers (III), which were obtained by reaction between  $\alpha$ -chloromethyl alkyl ethers (II) and ethylene oxide (I).

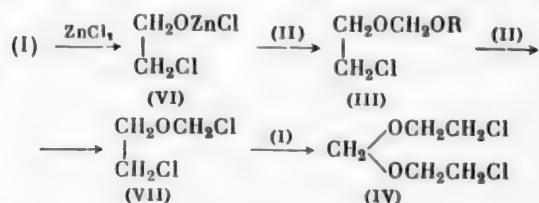


It was established that  $\alpha$ -chloro ethers react very slowly with ethylene oxide under ordinary conditions and that ethers (III) are obtained in low yields.

As our work showed, ethylene oxide reacts very vigorously with ethers (II) in the presence of anhydrous  $\text{ZnCl}_2$ , which requires conducting the reaction with cooling ( $-15$ – $-18^\circ$ ) as a result of which 35–85% yields of ethers (III) are obtained. Increasing reaction temperature ( $+10^\circ$ ) has a negative effect on the yield of (III) and increases the yield of symmetrization products (IV, V). The higher the molecular weight of (II), the lower is the yield of side products (IV, V).

However with branching in the alkyl chain of ether (II) the amount of side products sharply increases. For example,  $\alpha$ -chloromethyl butyl ether gives a greater yield of ether (III) (75–85%) than  $\alpha$ -chlorodimethyl ether (35–39%) and the by-products formed are 10 and 39% respectively.

By the reaction of (II,  $\text{R} = \text{CH}_3$ ) with methylene glycol methyl  $\alpha$ -chloroethyl ether methylene glycol  $\alpha$ -chloromethyl  $\beta$ -chloroethyl ether (VII) is obtained in 67.5% yield. Beginning with the above observation we showed that probably the reaction between a chloro ether and ethylene oxide in the presence of  $\text{ZnCl}_2$  goes by initial reaction of  $\text{ZnCl}_2$  with (I) to form a chlorozincalcoholate of ethylene chlorohydrin (VI) which with ether (II) give (III) and regenerated  $\text{ZnCl}_2$  for a new reaction cycle. Furthermore, an excess of  $\alpha$ -chloroether (II) with product (III) form a new  $\alpha$ -chloroether (VII), which reacts with ethylene oxide to form a symmetrization product (IV).

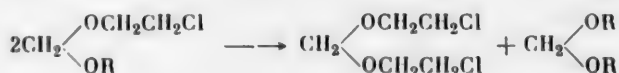


The symmetrization product (IV) can also be formed by reaction of (VI) with (VII).

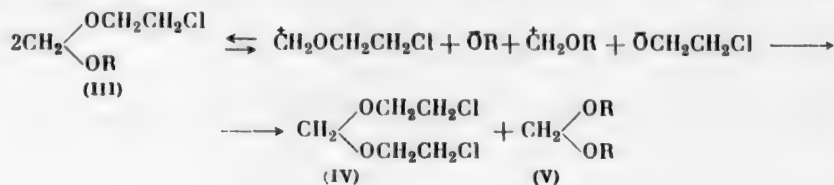
Consequently the main source for forming the symmetrization product (IV) is the reaction between  $\alpha$ -chloro-ether (II) and reaction product (III). Therefore the smaller the alkyl radical (II), i.e., the more active the  $\alpha$ -chloro-ether, the more (IV) is formed.

Experiments showed that compound (III) upon long storage (3 months) under diffuse light spontaneously undergoes symmetrization with formation of methylene glycol dialkyl ethers (V) (8-55%) and (IV) (8-55%). In the presence of  $\text{ZnCl}_2$  symmetrization of ether (III) is complete within several hours (4-10 hr) at ordinary temperatures, but in a few minutes (~15 min) upon heating in the presence of  $\text{ZnCl}_2$ .

The general reaction course for spontaneous symmetrization can be represented by the following equation:



The mechanism for spontaneous symmetrization of ethers (III) can be explained by assuming the molecules dissociate into ions and exchange with alkoxy radicals forming symmetrical ethers according to the scheme.



The rate of spontaneous symmetrization of ethers (III) depends on both the molecular weight and the structure of the alkyl radical of the alkoxy group.

With increasing molecular weight for the alkyl radical group in ether (III) the rate for spontaneous symmetrization falls; and, inversely, in the case of iso-alkyl structures in the alkoxy group, symmetrization both during synthesis and during storage is markedly accelerated, which is seen graphically from the yields of symmetrization products (Table 1) (IV, V).

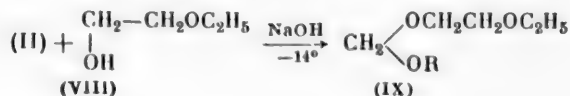
Apparently formation of ethers (IV, V) during synthesis of ether (III) is also connected with spontaneous symmetrization of ether (III).

Partial symmetrization occurs during fractionation of ethers (III) from a flask with a tall fractionating column (height 20-25 cm), as a result of which it becomes difficult to maintain the true boiling point; consequently the fractions have wide (5-8°) boiling point intervals.

To establish the structure of ethers (III), in addition to a series of chemical reactions, they were synthesized by the reaction of ethers (II) with chlorohydrin [2].



The character of the substituents found in the  $\beta$ -position of the simple methylene glycol ethers substantially influences the rate at which the asymmetric ethers symmetrize. Thus, for example, methylene glycol alkyl  $\beta$ -ethoxyethyl ethers (IX) which we synthesized by reacting (II) with ethylene glycol monoethyl ether (VIII) [2] are obtained almost entirely without product symmetrization.



However, symmetrization of ethers (IX) can be brought about by heating them in the presence of  $\text{ZnCl}_2$  or dimethylaniline hydrochloride, although symmetrization occurs to a small extent (1.5-3%) on standing.

Hence, an ethoxy group in the position  $\beta$  to the ether (IX) shows a much weaker influence on symmetrization than a chlorine atom in ethers (III). Further studies showed that some of the substances synthesized possess biological activity, the results of which will be published separately.



TABLE 1. Methylene Glycol Alkyl  $\beta$ -Chloroethyl Ethers  $\text{CH}_3\text{OCH}_2\text{CH}_2\text{Cl}$   
OR

No.	R	Boiling point (pressure in mm)	$n_D^{20}$	$d_4^{20}$	Empirical formula	$M_R$		C %		H %		Cl %		yield of symmetriza- tion products (in %)	yield of (IV) and (V)
						found	calc.	found	calc.	found	calc.	found	calc.		
1	$\text{CH}_3^*$	38—38.5° (15)	1.4196	1.0956	$\text{C}_4\text{H}_9\text{O}_2\text{Cl}$	28.99	28.82	38.58	38.50	7.37	7.32	28.28	28.50	36.1	39.3
2	$\text{C}_2\text{H}_5$	36—37 (8)	1.4206	1.0466	$\text{C}_5\text{H}_{11}\text{O}_2\text{Cl}$	33.53	33.44	42.80	43.32	8.01	7.94	25.05	25.63	41.3	34.7
3	$n\text{-C}_3\text{H}_7$	52—53 (10)	1.4243	1.0152	$\text{C}_6\text{H}_{13}\text{O}_2\text{Cl}$	38.37	38.06	46.77	47.20	8.32	8.52	23.10	23.28	62.6	28.0
4	$\text{iso-C}_3\text{H}_7$	40—41 (10)	1.4208	1.0140	$\text{C}_6\text{H}_{13}\text{O}_2\text{Cl}$	38.23	38.06	47.38	47.20	8.21	8.52	23.47	23.21	29	45.6
5	$n\text{-C}_4\text{H}_9$	55—55.5 (1)	1.4268	0.9982	$\text{C}_7\text{H}_{15}\text{O}_2\text{Cl}$	42.86	42.68	50.67	50.45	9.28	9.07	21.32	21.32	83.4	10.6
6	$\text{iso-C}_4\text{H}_9$	48.5 (2)	1.4256	0.9972	$\text{C}_7\text{H}_{15}\text{O}_2\text{Cl}$	42.74	42.68	50.13	50.45	9.13	9.07	21.53	21.32	73	18.9
7	$\text{iso-C}_5\text{H}_{11}$	74—75.5 (2)	1.4300	0.9797	$\text{C}_8\text{H}_{17}\text{O}_2\text{Cl}$	47.66	47.29	53.29	53.18	9.69	9.41	19.31	19.66	81	7.9

\* Literature data [3]: B.p. 130–136.8°;  $[\eta]$ : 135–138°

TABLE 2. Methylene Glycol Alkyl  $\beta$ -Ethoxyethyl Ethers  $\text{CH}_3\text{OCH}_2\text{CH}_2\text{OC}_2\text{H}_5$   
OR

No.	R	Boiling point (pressure in mm)	$n_D^{20}$	$d_4^{20}$	Empirical formula	$M_R$		C %		H %		Yield (in %)	
						found	calc.	found	calc.	found	calc.	found	calc.
1	$\text{CH}_3^*$	64.5—66° (44)	1.4008	0.9297	$\text{C}_6\text{H}_{14}\text{O}_3$	34.67	34.83	53.62	54.08	10.58	10.84	10.44	60
2	$\text{C}_2\text{H}_5$	75 (32)	1.4038	0.9139	$\text{C}_7\text{H}_{16}\text{O}_3$	39.83	39.45	56.55	56.84	11.00	10.81	10.81	69
3	$n\text{-C}_3\text{H}_7$	66—66.5 (8)	1.4085	0.9099	$\text{C}_8\text{H}_{18}\text{O}_3$	44.35	44.07	59.23	59.05	11.27	11.35	11.11	78
4	$\text{iso-C}_3\text{H}_7$	67—67.5 (20)	1.4035	0.8970	$\text{C}_8\text{H}_{18}\text{O}_3$	43.69	44.07	59.08	59.17	11.36	11.09	11.11	65
5	$n\text{-C}_4\text{H}_9$	69—70 (5)	1.4125	0.8928	$\text{C}_9\text{H}_{20}\text{O}_3$	48.30	48.688	61.15	62.36	11.30	11.36	11.36	81
6	$\text{iso-C}_4\text{H}_9$	60.5—61 (5)	1.4105	0.8905	$\text{C}_9\text{H}_{20}\text{O}_3$	48.90	48.68	61.90	61.49	11.61	11.80	11.36	76
7	$\text{iso-C}_5\text{H}_{11}$	72—73 (3)	1.4164	0.8903	$\text{C}_{10}\text{H}_{22}\text{O}_3$	53.59	53.30	63.05	63.15	11.20	11.57	11.57	79
8	$\text{OCH}_2\text{CH}_2\text{OC}_2\text{H}_5$	72—73 (2)	1.4162	0.9534	$\text{C}_9\text{H}_{20}\text{O}_4$	50.04	50.33	56.10	56.25	10.10	10.41	10.41	63.7

\* Literature data [6]: B.p. 163–164° (746 mm),  $n_D^{20}$  1.3940,  $d_4^{20}$  0.8972.

## EXPERIMENTAL PART

Methylene Glycol Ethyl  $\beta$ -Chloroethyl Ether (III,  $R = C_2H_5$ ). Ethylene oxide (15 g) was introduced into a mixture of 31.6 g of  $\alpha$ -chloromethyl ethyl ether in 100 ml of absolute ether containing 1 g of anhydrous  $ZnCl_2$  with cooling ( $-18^\circ$ ) and continuous stirring over a period of 4 hr. The reaction mixture was left overnight; after washing, drying, and distilling the solvent 19 g (41.3%) of ether (III,  $R = C_2H_5$ ), the constants for which are given in Table 1 (compound 2), 5.0 g of methylene glycol diethyl ether [4] and 10 g (34.7%) of methylene glycol  $\beta, \beta'$ -dichloroethyl ether (IV) were isolated.

B.p.  $80-82^\circ$  (1 mm),  $d_4^{20}$  1.2129,  $n_D^{20}$  1.4540;  $MR_D$  38.62; Calculated 38.31 [5].

Found %: C 35.00, 34.60; H 6.04, 5.56; Cl 41.45, 41.23.  $C_5H_{10}O_2Cl_2$ . Calculated %: C 34.60; H 5.78; Cl 41.04.

Six more new representative methylene glycol alkyl  $\beta$ -chloroethyl ethers, the constants for which are presented in Table 1, were synthesized under analogous conditions.

Methylene Glycol Methyl  $\beta$ -Chloroethyl Ether (III,  $R = CH_3$ ).  $\alpha$ -Chloromethyl ether (40 g) was added to a mixture of 30 g of powdered NaOH, 50 g of anhydrous ether, and 40 g of ethylene chlorohydrin over a period of 1 hr with good cooling ( $-14^\circ$ ) and stirring. Stirring was then continued 2 hr more, after which the reaction mixture was diluted with water. After drying and distilling the solvent the product was distilled under vacuum; 40 g (65%) of an ether, the constants for which agree with data from experiment (A) given in Table 1 (compound 1) was obtained; formation of methylene glycol  $\beta, \beta'$ -dichloroethyl ether did not occur. Methylene glycol ethyl  $\beta$ -chloroethyl, and *n*-propyl  $\beta$ -chloroethyl ethers were synthesized by analogous routes in yields of 75 and 88%, respectively.

Symmetrization of Methylene Glycol Methyl  $\beta$ -Chloroethyl Ether (III,  $R = CH_3$ ) under Ordinary Conditions. The ether (20 g) (III,  $R = CH_3$ ) was sealed in an ampule and left in diffuse light for 3 months. Then the ampule was opened and the contents were distilled, from which 3.5 g of methylene glycol dimethyl ether (b.p.  $40-42^\circ$ ), 7.2 g of asymmetric ether, and 8.2 g of symmetric ether (IV) (b.p.  $80-82.5^\circ$  at 1 mm),  $d_4^{20}$  1.2120,  $n_D^{20}$  1.4545 were obtained.

Reaction of Anhydrous  $ZnCl_2$  with Ether (III,  $R = CH_3$ ) under Ordinary Conditions. The ether (20 g) and 0.05 g of anhydrous  $ZnCl_2$  were left for 4 hr; then 1.0 g of NaOH in powder form was added to the flask and the contents were distilled. Dimethylal (3.8 g) distilled first at  $40-43^\circ$ . The residue was washed with water and after drying distilled under vacuum. Unchanged starting material (6.0 g) and 8.3 g of ether (IV) were obtained.

Symmetrization of Ether (III,  $R = CH_3$ ) by Heat. The Ether (25 g) was heated to  $120^\circ$  in a flask equipped with a herringbone fractionating column (height 20 cm). Methylene glycol dimethyl ether (4.5 g) was distilled during 3 hr. The residue was distilled under vacuum, as a result of which 7.2 g of unchanged starting material and 10.9 g of ether (IV) were obtained.

Symmetrization of Ether (III,  $R = CH_3$ ) with Anhydrous  $ZnCl_2$  and Heat. The ether (25 g) and 0.05 g of anhydrous  $ZnCl_2$  was heated at  $45^\circ$  (44 mm) for 15 minutes. Then 1.0 g of powdered NaOH was added to the flask and the product was distilled under vacuum; 16.6 g of ether (IV) was isolated.

Reaction of  $\alpha$ -Chloroethyl Ether with Methylene Glycol Dibutyl Ether. A mixture of 20 g of chloro ether (II,  $R = CH_3$ ) and 25 g of dibutyl ether was charged into a flask with a herringbone fractionating column. This was heated on a water bath at  $45-50^\circ$ . The ether (8.5 g) (V,  $R = CH_3$ ) distilled at  $40-42^\circ$ . The residue was distilled under vacuum. The  $\alpha$ -chloromethyl butyl ether (22.8 g; 75%) boiling at  $131-134^\circ$ ,  $d_4^{20}$  0.9520 was isolated.

The reaction of the  $\alpha$ -chloromethyl ether with methylene glycol methyl butyl ether was conducted in the same manner;  $\alpha$ -chloromethyl butyl ether was isolated in 70% yield; the dibutyl ether, the symmetrization product from methylene glycol methyl butyl ether, was also formed.

Reaction of  $\alpha$ -Chloromethyl Ether with Methylene Glycol Methyl  $\beta$ -Chloroethyl Ether. A mixture of 20 g of chloroether (II,  $R = CH_3$ ) and 25 g of ether (III,  $R = CH_3$ ) was charged to a flask with a herringbone fractionating column. This was heated on a water bath at  $45-55^\circ$ ; a product (18.5 g) gradually distilled and was purified from partially distilled  $\alpha$ -chloromethyl ether by reaction with dimethyl aniline; the mixture was subjected to distillation. Methylene glycol dimethyl ether (14.3 g) was isolated (b.p.  $40-42^\circ$ ). The liquid portion remaining in the flask after distillation was further distilled; 17.5 g (67.5%) of  $\alpha$ -chloromethyl  $\beta$ -chloroethyl ether (VII) boiling at  $153-155^\circ$ ,  $d_4^{20}$  1.2806 [5]; and 4.9 g (28.8%) of ether (IV), which is indicative of partial symmetrization of the methyl  $\beta$ -chloroethyl ether under the reaction conditions, were isolated.

Methylene glycol  $\alpha$ -chloromethyl  $\beta$ -chloroethyl and dimethyl ethers were obtained in the same way by reaction between  $\alpha$ -chloromethyl ether and methylene glycol  $\beta, \beta'$ -dichloroethyl ether.

Methylene Glycol Methyl  $\beta$ -Ethoxyethyl Ether (IX, R = CH<sub>3</sub>). In a round-bottomed flask equipped with a reflux condenser and mechanical stirrer, 27 g of methylene glycol monomethyl ether (VIII) dissolved in 50 ml of dry ether was added to 20 g of powdered KOH; then 27 g of  $\alpha$ -chloromethyl ether was added with cooling (-12 -14°) to the reaction mixture. After the usual work-up 27.38 g (68%) of ether (IX, R = CH<sub>3</sub>), constants for which are given in Table 2, was isolated.

No symmetrization product was detected.

More new representative methylene glycol alkyl alkoxyethyl ethers, the constants for which are given in Table 2, were obtained under similar conditions.

#### SUMMARY

1. Fourteen new methylene glycol ethers were synthesized and their properties were studied.
2. It was established that alkyl  $\beta$ -chloroethyl ethers undergo symmetrization with formation of  $\beta, \beta'$ -dichloroethyl ether both under synthesis conditions and partially spontaneously; the latter is isolated as a side product; the amount of it increases with decreasing molecular weight of the  $\alpha$ -chloroether used for the reaction.
3. Mechanisms for the symmetrization reaction of alkyl  $\beta$ -chloroethyl ethers under different conditions were proposed.
4. It was established that an ethoxy group in the  $\beta$ -position, in contrast to a chlorine atom, has little effect on the symmetrization of asymmetric methylene glycol ethers.

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3. U. S. patent 2359134 (1944).
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# STUDIES OF GLYCOL ETHERS AND THEIR DERIVATIVES

## XXXVIII. SYNTHESIS OF ALKOXY DERIVATIVES OF GLYCERYL

### METHYL ETHERS

Shamkhal Mamedov and M. A. Avanesyan

Institute for Petrochemical Processes,

Academy of Sciences, Azerbaidzhan SSR

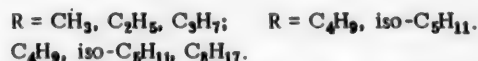
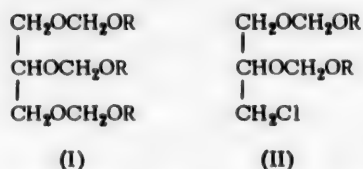
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 11,

pp. 3566-3571, November, 1961

Original article submitted August 17, 1960

It was previously shown that simple haloethers possess insecticidal [1, 2] and acaricidal properties [3].

The synthesis of alkoxy derivatives of glyceryl methyl ether and glycerine chlorohydrins seemed interesting. We obtained alkoxy derivatives of glyceryl methyl ether (I) by the "caustic" method of reacting  $\alpha$ -chloroethers with anhydrous glycerine in the presence of dimethylaniline [4].

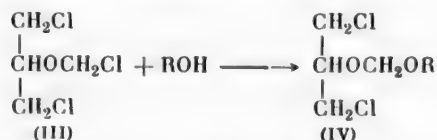


Alkoxy derivatives of glycerine chlorohydrin monomethyl ether (II) were obtained under similar conditions.

It was established that in synthesis of alkoxy ethers (I) it is expedient to take an excess (15-20%) of the  $\alpha$ -chloroether in order to avoid forming glyceryl monoalkoxymethyl and dialkoxymethyl ethers as side products. For synthesizing alkoxy derivatives of glycerine chlorohydrin methyl ether it is sufficient to take a small excess (5-10%) of the  $\alpha$ -chloroether. Mono and dialkoxy derivatives of glyceryl methyl ether can be obtained by the same method [4]. Some excess of  $\alpha$ -chloroether (10%) and dimethylaniline (12%), as our experiments showed, give better results, and in the given case, moreover, mono- and dialkoxy derivatives of glyceryl methyl ether are convenient starting materials for synthesis of mixed alkoxy derivatives of glyceryl methyl ethers.

A new  $\alpha$ -chloroether (III) was obtained from  $\alpha, \gamma$ -dichloroglycerine by method [4] in 59% yield; this has properties of ordinary  $\alpha$ -chloroethers.  $\alpha, \gamma$ -Dichloro glyceryl methylene glycol ether (IV) was obtained by reaction between  $\alpha$ -chloroether (III) and alcohol under conditions of the "caustic" method. The structure of this ester (IV) was demonstrated by its synthesis from the reaction between  $\alpha$ -chloroethers and dichloroglycerine.

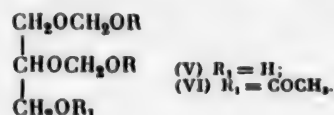
The constants of ether (IV) obtained by the different routes agreed.



It was further established that the constants for diisopentoxydimethyl glyceryl ether, given in the literature by V. Yasnopolskii et al. [5], (B.p. 265-285° at 5 mm,  $n_D^{20}$  1.4388,  $d_4^{20}$  0.9370), did not, in fact, correspond. Our experiments showed that this ether possessed a boiling point of 155-157° (4 mm);  $n_D^{20}$  1.4373;  $d_4^{20}$  0.9640. Constants for glyceryl monooxymethyl ether ( $n_D^{20}$  1.4345,  $d_4^{20}$  0.8574), given in the same reference [5], were also incorrect. Mono-

octoxymethyl glyceryl ether, which we synthesized, had the constants:  $n_D^{20}$  1.4492,  $d_4^{20}$  0.9880. This is apparently explained by the fact that the authors in the experiment allowed a wide boiling range for the "individual" ethers (20°) and a large variance in molecular refraction (7.35), and did not consider the variance in carbon analyses (2.15%).

We studied the chemical conversions of some of the alkoxy derivatives of glyceryl methyl ethers and glycerine chlorohydrins. It was established that by reaction of acetic anhydride with dibutoxydimethyl glyceryl ether (V) the ester (VI) was obtained in 55% yield; this was saponified with alcoholic caustic to give back the starting ether (V).



Ester (VI) was also obtained by reaction between acetyl chloride and the alkoxy ether (V) in the presence of dimethylaniline. The constants for ether (VI) obtained by different routes agrees. Attempted condensation of formaldehyde with ether (V) without catalyst participation (HCl) did not give positive results, but in the presence of hydrochloric acid partial hydrolysis of starting material (V) occurred with formation of monoalkoxymethyl glyceryl ether.

On prolonged heating (36 hr) of diisopentoxydimethyl ether of  $\alpha$ -glycerine chlorohydrin (II) with caustic (20%) and with sodium methoxide, the chlorine atom was not displaced by hydroxide, which confirms the stable condition of the chlorine atom in that ether.

Biological tests conducted with the alkoxy glycerine derivatives and glycerine chlorohydrins synthesized showed that they were biologically active compounds. Some of them [6] exhibited insecticidal properties against blight for cotton and other plants, at the same time being only slightly toxic to warm-blooded animals.

#### EXPERIMENTAL PART

**Trimethoxytrimethyl Glyceryl Ether (I,  $R = \text{CH}_3$ ).** To a mixture of 18.4 g of anhydrous glycerine [7] and 150 g of dimethylaniline dissolved in 80 ml of anhydrous benzene was added 90 g of  $\alpha$ -chloromethyl ether in drops with mixing and cooling (20-22°). Then stirring was continued at 40-50° for 2 hr more. Then water was added to the reaction mixture until the residue completely dissolved. The benzene extract was washed with a 5%  $\text{H}_2\text{SO}_4$  solution, with saturated  $\text{Na}_2\text{CO}_3$  solution, and with water. After drying and distilling the solvent 32 g (71%) of the ether, the constants for which are given in Table 1 (compound 1), was isolated by vacuum distillation. Six new examples of ethers of type (I) were obtained under similar conditions (Table 1).

**Diethoxymethyl Glyceryl Ether.** From 16 g of glycerine, 85 g of dimethylaniline, and 62 g of  $\alpha$ -chloroethyl ether in 100 ml of benzene under conditions of the previous experiment, 21 g (58%) of ether, the constants for which are given in Table 2 (compound 1), was obtained. Four more new representative ethers (VIII) were synthesized under similar conditions.

**Monooctoxymethyl Glyceryl Ether ( $n$ -prim- $\text{C}_8\text{H}_{17}$ ).** From 18.4 g of glycerine, 39.2 g of  $\alpha$ -chloromethyloctyl ether, and 28 g of dimethylaniline in 100 ml of benzene as medium was obtained 9 g (19.6%) of the ether by the general route.

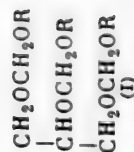
B.p. 204-206° (17 mm),  $n_D^{20}$  1.4492,  $d_4^{20}$  0.9880,  $\text{MR}_D$  63.55; Calculated 63.95.

Found %: C 61.33, 61.14, H 11.40, 11.38.  $\text{C}_{12}\text{H}_{26}\text{O}_4$ . Calculated %: C 61.53; H 11.11.

**Dibutoxydimethyl Ether of Glycerine  $\alpha$ -Monochlorohydrin of Glycerine (II,  $R = n\text{-C}_4\text{H}_9$ ).** From 11 g of glycerine  $\alpha$ -monochlorohydrin [8], 27.8 g of dimethylaniline, and 26.8 g of  $\alpha$ -chloromethylbutyl ether in 100 ml of benzene, 17.5 g of an ether, the constants for which are given in Table 2 (compound 6), was obtained by the general method. The diisopentoxydimethyl ether of glycerine  $\alpha$ -chlorohydrin the constants for which are given in Table 2 (compound 7), was synthesized under similar conditions.

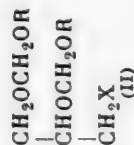
**$\alpha$ -Chloromethyl-  $\beta$ ,  $\beta'$ -dichloroisopropyl Ether (III).** HCl was passed through a mixture consisting of 560 g of glycerine  $\alpha$ ,  $\gamma$ -dichlorohydrin and 400 g of trioxymethylene (50%) at -5° until HCl absorption stopped (15 hr). Then the lower layer was separated from the top water layer and dried over  $\text{CaCl}_2$ . The  $\alpha$ -chloroether (III), (455 g; 59%) was separated by vacuum distillation.

TABLE 1. Alkoxy Derivatives of Glyceryl Methyl Ethers (I)



No.	R	Boiling point (pressure in mm)	$n_D^{20}$	$d_4^{20}$	MRD		C	H	Empirical formula	Calc. (%)		Yield (in %)
					Found	Calc.				C	H	
1	CH <sub>3</sub>	111-113° (6)	1.4226	1.0664	53.39	53.62	48.66, 48.85	9.05, 9.34	C <sub>3</sub> H <sub>20</sub> O <sub>6</sub>	48.21	8.92	71
2	C <sub>2</sub> H <sub>5</sub>	112-114 (2)	1.4212	1.0018	67.32	67.47	54.68, 54.61	10.10, 10.03	C <sub>13</sub> H <sub>28</sub> O <sub>6</sub>	54.13	9.77	80
3	n-C <sub>3</sub> H <sub>7</sub>	150-152 (2)	1.4258	0.9661	81.78	81.33	58.10, 58.85	10.85, 10.67	C <sub>15</sub> H <sub>32</sub> O <sub>6</sub>	54.44	10.38	77.9
4	n-C <sub>4</sub> H <sub>9</sub>	169-171 (4)	1.4315	0.9535	95.11	95.18	61.31, 61.40	11.09, 11.02	C <sub>18</sub> H <sub>38</sub> O <sub>6</sub>	61.71	10.85	69
5	iso-C <sub>4</sub> H <sub>9</sub>	166-167 (4)	1.4278	0.9450	95.35	95.18	61.52, 61.30	11.20, 11.03	C <sub>18</sub> H <sub>38</sub> O <sub>6</sub>	61.71	10.85	71
6	iso-C <sub>5</sub> H <sub>11</sub>	176-177 (4)	1.4350	0.9388	108.95	109.03	64.22, 64.19	11.58, 11.63	C <sub>21</sub> H <sub>46</sub> O <sub>6</sub>	64.38	11.22	75
7	n-primary C <sub>8</sub> H <sub>17</sub>	263-264 (3)	1.4448	0.9170	150.15	150.59	68.89, 68.93	11.51, 12.38	C <sub>30</sub> H <sub>62</sub> O <sub>6</sub>	69.49	11.96	34.7

TABLE 2. Dialkoxy Derivatives of Methyl Ethers of Glycerine α - Monochlorohydrin (II)



No.	R	X	Boiling point (pres- sure in mm)	$n_D^{20}$	$d_4^{20}$	MRD		Found (%)			Empirical formula	Calc. (%)			Yield (in %)
						Found	Calc.	C	H	Cl		C	H	Cl	
1	C <sub>2</sub> H <sub>5</sub>	OH	140-142° (10)	1.4208	1.0192	51.72	51.86	51.54, 51.46	10.15, 9.99		C <sub>9</sub> H <sub>20</sub> O <sub>5</sub>	51.92	9.64		58
2	n-C <sub>4</sub> H <sub>9</sub>	OH	150-151 (5)	1.4347	0.9818	70.17	70.33	58.91, 58.61	11.11, 11.01		C <sub>13</sub> H <sub>28</sub> O <sub>5</sub>	59.09	10.60		45
3	iso-C <sub>4</sub> H <sub>9</sub>	OH	145-146 (4)	1.4316	0.9702	70.46	70.33	58.70, 58.75	11.02, 11.09		C <sub>13</sub> H <sub>28</sub> O <sub>5</sub>	59.09	10.60		38
4	iso-C <sub>5</sub> H <sub>11</sub>	OH	155-157 (4)	1.4373	0.9640	79.39	79.57	61.54, 61.55	11.43, 11.48		C <sub>17</sub> H <sub>32</sub> O <sub>5</sub>	61.64	10.95		51
5	n-primary C <sub>8</sub> H <sub>17</sub>	OH	222-224 (2)	1.4469	0.9340	107.63	107.27	66.71, 66.86	12.01, 12.21		C <sub>21</sub> H <sub>46</sub> O <sub>5</sub>	67.02	11.70		42.5
6	n-C <sub>4</sub> H <sub>9</sub>	Cl	138-140 (3)	1.4377	1.0127	73.16	73.67	55.30, 55.60	9.57, 9.68	12.74, 12.80	C <sub>13</sub> H <sub>27</sub> O <sub>5</sub> Cl	55.22	9.55	12.56	62
7	iso-C <sub>5</sub> H <sub>11</sub>	Cl	154-155 (5)	1.4411	0.9900	82.85	82.91	57.83, 57.97	10.58, 10.47	11.87, 11.47	C <sub>17</sub> H <sub>31</sub> O <sub>5</sub> Cl	57.97	9.98	11.43	59



B.p. 70-73° (4 mm),  $n_D^{20}$  1.4810,  $d_4^{20}$  1.386,  $MR_D$  36.44.  $C_4H_7OCl_3$ . Calculated 36.91

Butoxymethyl Ether of Glycerine  $\alpha$ ,  $\gamma$ -Dichlorohydrin (IV,  $R=n-C_4H_9$ ). a) The ether (45 g; 42%) was obtained from 69.5 g of dimethylaniline, 67 of  $\alpha$ -chloromethylbutyl ether, and 64.5 g of glycerine  $\alpha$ ,  $\gamma$ -dichlorohydrin after two vacuum distillations.

B.p. 118-119° (15 mm),  $n_D^{20}$  1.4512,  $d_4^{20}$  1.1037,  $MR_D$  52.49; Calculated 52.16.

Found %: C 44.16, 44.29; H 7.70, 7.65; Cl 32.73, 32.69.  $C_9H_{16}O_2Cl_2$ . Calculated %: C 44.65; H 7.44; Cl 32.03.

b) The same ether was obtained in 34% yield from 44 g of  $\alpha$ -chloroether (III), 40 g of n-butyl alcohol, and 40 g of dimethylaniline under conditions of the "caustic" method. The constants agreed with those given in experiment (a).

Reaction of Acetic Anhydride with Dibutoxydimethyl Glyceryl Ether (V,  $R=n-C_4H_9$ ). A mixture of 47 g of ether (V; and 80 g of acetic anhydride was heated (120-130°) for 5 hr. After washing and drying, 30 g (55%) of dibutoxydimethyl glyceryl ether acetate (VI) was obtained by distillation.

B.p. 170-172° (6 mm),  $n_D^{20}$  1.4290,  $d_4^{20}$  0.9962,  $MR_D$  79.31.  $C_{15}H_{30}O_6$ . Calculated 79.69.

The same ester (VI) was obtained in 38.5% yield by reaction between 20 g of acetyl chloride and 33 g of ether (V) under conditions for the caustic method [4]. The constants agreed with those given in the previous experiment.

Saponification of Dibutoxydimethyl Glyceryl Ether Acetate (VI). To a solution of 10 g of NaOH in 50 ml of water was added 30 g of ether (VI) and 50 ml of methanol. The mixture was heated (50-60°) for 4 hr. It was then diluted with water and the product extracted with ether. After drying and distilling the solvent 10 g (37.8%) of ether (V) was obtained.

#### SUMMARY

1. Twelve new alkoxy derivatives of glyceryl methyl ethers and glycerine chlorohydrin were synthesized and their physical and chemical constants were presented.
2. It was shown that the chlorine atom in alkoxy derivatives of glycerine chlorohydrin methyl ether is very stable.
3. It was established that alkoxy derivatives of glyceryl methyl ether have biological activity.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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THE SYNTHESIS OF GEOMETRICAL ISOMERS  
OF 1,2,5-TRIMETHYL-4-HYDROXY-4-PIPERIDYLMETHYLARYL-  
AND 1,2,5-TRIMETHYL-4-HYDROXY-4-PIPERIDYLDIARYL  
CARBINOLS

B. V. Unkovskii, I. A. Mokhir, and S. G. Batrakov

M. V. Lomonosov Moscow Institute of Fine Chemical Technology

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The preparation of geometrical isomers of 1,2,5-trimethyl-4-carbomethoxy-4-piperidol ( $1\alpha$ ,  $\beta$ ,  $\gamma$ ) [1, 2] and 1,2,5-trimethyl-4-acetyl-4-piperidol ( $II\alpha$ ,  $\beta$ ,  $\gamma$ ) [2, 3] as starting materials for the synthesis of various compounds with potential anesthetic activity [4, 5] which are stereoisomeric analogs of  $\alpha$ - and  $\beta$ -eucaines [6], has been described in previous communications from our laboratory.

The present study, which was undertaken at the suggestion of the late I. N. Nazarov, describes stereoisomeric  $\alpha$ -glycols of the piperidine series which were prepared by the reaction of stereoisomeric hydroxyesters ( $I\alpha$ ,  $\beta$ ,  $\gamma$ ) and ketoalcohols ( $II\alpha$ ,  $\beta$ ,  $\gamma$ ) with organometallic compounds. These piperidine pinacols are of interest as intermediates for the synthesis of new compounds with anodyne activity which are stereoisomeric analogs of ketobemidone [7] one of the most active synthetic substitutes for morphine.

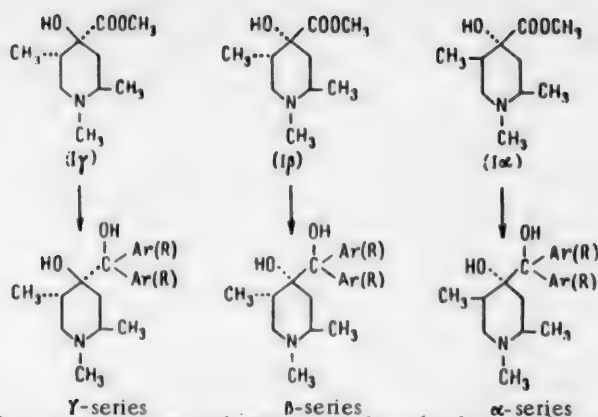
The reaction of organometallic compounds with geometrical isomers of 1,2,5-trimethyl-4-carbomethoxy-4-piperidol ( $I\alpha$ ,  $\beta$ ,  $\gamma$ ) makes it possible to prepare stereoisomeric 1,2,5-trimethyl-4-hydroxy-4-piperidinyldialkyl- and 1,2,5-trimethyl-4-hydroxy-4-piperidyldiarylcarbinols (III-XI) in high yields. Organolithium compounds were preferred for this purpose since, as a rule, they give higher yields of glycols than the corresponding alkylmagnesium halides and arylmagnesium halides. In this way three isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidyldiphenylcarbinol ( $VI\alpha$ ,  $\beta$ ,  $\gamma$ ) were prepared from stereoisomeric hydroxyesters ( $I\alpha$ ,  $\beta$ ,  $\gamma$ ) and phenyl lithium. In synthesizing stereoisomeric 1,2,5-trimethyl-4-hydroxy-4-piperidyl-di(p-methoxyphenyl)- and 1,2,5-trimethyl-4-hydroxy-4-piperidyl-di(p-ethoxyphenyl)-carbinols ( $X\beta$ ,  $\gamma$ ) and ( $XI\beta$ ,  $\gamma$ ), in order to avoid anomalous reactions that are associated with the preparation of alkoxy-substituted aryl lithiums [8], the corresponding arylmagnesium halides were used.

Along with these compounds, pinacol (VII), (VIII) and (IX) with other substituents in the aromatic rings in the para and meta positions, were also obtained. The method we used offers the possibility, without any significant limitations, of synthesizing various piperidine  $\alpha$ -glycols of varying character and degree of substitution.

With the exception of the stereoisomeric carbinols ( $VI\alpha$ ,  $\beta$ ,  $\gamma$ ), that were synthesized in three out of the four theoretically possible diastereoisomeric forms, for all the remaining pinacol there were principally prepared, as the most practicable, geometrical isomers belonging to the  $\beta$ - and  $\gamma$ -configurational series. In the case of the glycols (IV), (V), (VIII) and (IX), which are of less interest from a preparative point of view, only the  $\gamma$ -isomers were synthesized.

Since the synthesis of the stereoisomeric pinacol (III-XI) from the geometrical isomers of 1,2,5-trimethyl-4-carbomethoxy-4-piperidol ( $I\alpha$ ,  $\beta$ ,  $\gamma$ ) proceeds without affecting the asymmetric center and is not accompanied by epimerization of the  $C_4$  of the piperidine ring, the stereoisomeric compounds described are given the spatial configuration of the corresponding geometrical isomers of the original hydroxyester (I) [9].

The pinacols described are colorless crystalline substances with the exception of compounds ( $III\beta$ ), ( $X\beta$ ) and ( $XI\beta$ ) which were obtained in the form of viscous liquids. The properties of the stereoisomeric 1,2,5-trimethyl-4-hydroxy-4-piperidyldialkyl- and 1,2,5-trimethyl-4-hydroxy-4-piperidyldiarylcarbinols (III-XI) and their derivatives are shown in Table 1.



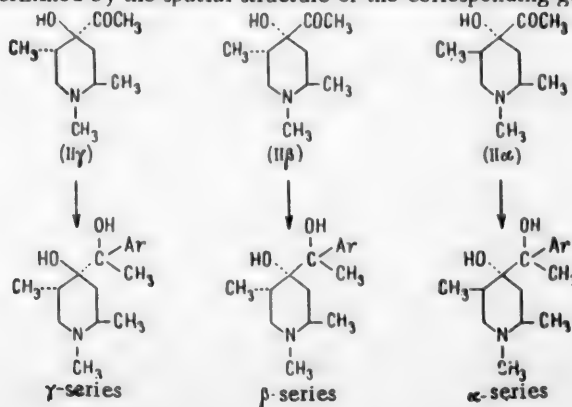
The glycols (VI–XI), which contain aromatic substituents in the side chain at the carbinol carbon atom, are similar in structure and chemical behavior to the pseudobasic dyes of the triphenylmethane series and like them form colored salts when treated with concentrated mineral acids. The most characteristic halochromic phenomenon appears in the case of glycols (IX), (X) and (XI) where at first a green coloration is observed which, on dilution with water or alcohol, passes through sky-blue to dark blue and violet, while in the case of pinacol (X) and (XI) there is a bright red coloring which disappears when water or alcohol is added. Glycols (VI), and (VII) and (VIII) form easily hydrolyzed yellow salts.

On crystallizing the colored salts (for example the impure hydrochlorides) from polar solvents, completely colorless compounds are obtained.

In the light of present concepts on the dependence of color on structure, the reaction of carbinols (VI–XI) with mineral acids should lead to salt formation both at the amino group of the piperidine ring and at the carbinol function, in view of the acid-base reaction, with the formation of a salt with a complex organic cation of carbonium structure [10]. The appearance of bright coloration in the salts of carbinols (IX), (X) and (XI), in contrast to the weak coloration of the salts of glycols (VI), (VII) and (VIII) must be explained by the strengthening of the basic properties of the carbinol carbon atom under the influence of the dimethylamino and alkoxy groups located in the para positions of the aromatic rings which play the role of auxochromic groups. As would follow from our hypotheses, carbonium salts formed from glycols (VI–VIII) and also from (X) and (XI) hydrolyze very easily, while salts formed from carbinol (IX) are much more stable in this respect.

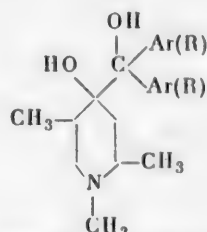
The reaction of geometric isomers of 1,2,5-trimethyl-4-acetyl-4-piperidol ( $\text{II}\alpha$ ,  $\beta$ ,  $\gamma$ ) with organolithium and magnesium compounds gives stereoisomers of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethylcarbinols (XII–XVI). Thus, from the stereoisomeric ketoalcohols ( $\text{II}\alpha$ ,  $\beta$ ,  $\gamma$ ) and phenyllithium, three isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethylphenylcarbinol ( $\text{XII}\alpha$ ,  $\beta$ ,  $\gamma$ ) were obtained. In an analogous manner, by using p-anisyl- and p-phenetylmagnesium bromides, three geometric isomers each of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-methoxyphenyl)- and 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-ethoxyphenyl)-carbinols ( $\text{XV}\alpha$ ,  $\beta$ ,  $\gamma$ ) and ( $\text{XVI}\alpha$ ,  $\beta$ ,  $\gamma$ ) were synthesized. Only the  $\gamma$ -isomers were obtained from glycols (XIII) and (XIV). The properties of the geometrical isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethylarylcarbinols (XII–XVI) and their derivatives are shown in Table 2. The behavior of these carbinols with mineral acids is analogous to that described for carbinols (VI–XI).

Organometallic synthesis in the case of stereoisomeric ketols ( $\text{II}\alpha$ ,  $\beta$ ,  $\gamma$ ), just as in the case of the hydroxyesters ( $\text{I}\alpha$ ,  $\beta$ ,  $\gamma$ ) proceeds without affecting the asymmetric center at the  $\text{C}_4$  of the piperidine ring. In consequence of this, the spatial configuration of the ring portion of the geometric isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethylarylcarbinols (XII–XVI) is determined by the spatial structure of the corresponding geometrical isomers of ketol (II) [9].



In view of the appearance of a new asymmetric center in the side chain, each geometrical isomer of ketoalcohol (II), as a result of organometallic synthesis, should form two isomeric glycols differing in the spatial arrangement of their substituents at the carbonyl carbon atom in relation to the rest of the molecule (erythro- and threo-isomers).

TABLE 1. Stereoisomeric 1,2,5-Trimethyl-4-Hydroxy-4-Piperidylalkyl- and 1,2,5-Trimethyl-4-Hydroxy-4-Piperidylarylcarbinols



No.	Ar (R)	Iso-mer	M.p.	solvent for recrystallization	yield (in %)	Empirical formula	% N	
							found	calc.
(III)	CH <sub>3</sub>	β	B.p. 95—97 °(2 mm)	—	68	C <sub>11</sub> H <sub>23</sub> O <sub>2</sub> N	6.60, 6.95	6.99
		γ	120—121	b	93	C <sub>11</sub> H <sub>23</sub> O <sub>2</sub> N	6.93, 6.68	6.99
		γ	ch 181—183	ac	—	C <sub>11</sub> H <sub>24</sub> O <sub>2</sub> NCl	5.65, 5.70	5.89
(IV)	C <sub>2</sub> H <sub>5</sub>	γ	147—148	b	88	C <sub>13</sub> H <sub>27</sub> O <sub>2</sub> N	5.78, 5.71	6.11
(V)	C <sub>3</sub> H <sub>7</sub>	γ	118—119	b	79	C <sub>15</sub> H <sub>31</sub> O <sub>2</sub> N	5.20, 5.37	5.45
		γ	ch 149—150	ac	—	C <sub>15</sub> H <sub>32</sub> O <sub>2</sub> NCl	4.89, 4.58	4.77
(VI)	C <sub>6</sub> H <sub>5</sub>	α	158—159	ac	50	C <sub>21</sub> H <sub>27</sub> O <sub>2</sub> N	4.29, 4.45	4.30
		α	ch 194—195	ac	—	C <sub>21</sub> H <sub>28</sub> O <sub>2</sub> NCl	3.93, 4.02	3.87
		β	233—233.5	b	78.5	C <sub>21</sub> H <sub>27</sub> O <sub>2</sub> N	4.29, 4.33	4.30
		β	ch 246—247	al + ac	—	C <sub>21</sub> H <sub>28</sub> O <sub>2</sub> NCl	3.69, 3.70	3.87
		γ	217—218	d	97.5	C <sub>21</sub> H <sub>27</sub> O <sub>2</sub> N	4.48, 4.03	4.30
		γ	ch 236—237	al	—	C <sub>21</sub> H <sub>28</sub> O <sub>2</sub> NCl	3.70, 3.79	3.87
		β	133—134	b	72	C <sub>23</sub> H <sub>31</sub> O <sub>2</sub> N	3.91, 4.04	3.96
		β	ch 247—248	ac + al	—	C <sub>23</sub> H <sub>32</sub> O <sub>2</sub> NCl	3.61, 3.56	3.59
(VII)	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	γ	243—244	ac	71.1	C <sub>23</sub> H <sub>31</sub> O <sub>2</sub> N	3.98, 4.20	3.96
		γ	ch 239—240	ac + al	—	C <sub>23</sub> H <sub>32</sub> O <sub>2</sub> NCl	3.80, 3.49	3.59
(VIII)	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	γ	213—214	ac + b	63.3	C <sub>23</sub> H <sub>31</sub> O <sub>2</sub> N	3.59, 3.70	3.96
		γ	ch 244—246	al	—	C <sub>23</sub> H <sub>32</sub> O <sub>2</sub> NCl	3.30, 3.33	3.59
(IX)	P-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	γ	221—222	b	68	C <sub>25</sub> H <sub>37</sub> O <sub>2</sub> N <sub>3</sub>	10.05, 10.22	10.21
		γ	ch 325—326	al	—	C <sub>25</sub> H <sub>40</sub> O <sub>2</sub> N <sub>3</sub> Cl <sub>3</sub>	7.79, 7.96	8.05
(X)	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	β	205—206	al	50	C <sub>23</sub> H <sub>32</sub> O <sub>4</sub> NCl	3.68, 3.44	3.32
		γ	205—206	CCl <sub>4</sub>	66.6	C <sub>23</sub> H <sub>31</sub> O <sub>4</sub> N	3.44, 3.66	3.64
		γ	ch 186—187	ac	—	C <sub>23</sub> H <sub>32</sub> O <sub>4</sub> NCl	3.46, 3.48	3.32
(XI)	p-C <sub>2</sub> H <sub>5</sub> OC <sub>6</sub> H <sub>4</sub>	β	208—209	al	57.9	C <sub>25</sub> H <sub>36</sub> O <sub>4</sub> NCl	3.27, 3.13	3.11
		γ	177—178	CCl <sub>4</sub>	77.5	C <sub>25</sub> H <sub>35</sub> O <sub>4</sub> N	3.28, 3.27	3.39

Note: b) benzene, al) alcohol, ac) acetone, d) dioxane, hy) hydrochloride

It is known that an asymmetric center located alongside the carbonyl group, in addition reactions with nucleophilic reagents (organometallic compounds for example), has an influence on the conformation of substituents at the newly formed asymmetric center [11]. In such cases a mixture of stereoisomeric compounds with a predominance of the thermodynamically more efficient erythro-isomers [12] is formed.

We found that the reaction of stereoisomeric ketoalcohols (II $\alpha$ ,  $\beta$ ,  $\gamma$ ) with organometallic compounds is even more spatially oriented and, in consequence, each geometrical isomer of ketol (II) forms a single diastereoisomeric glycol. In no case was it possible to detect the presence of other stereoisomeric forms in the reaction products. As can be seen from the results obtained, the presence of a piperidine ring in ketols (II $\alpha$ ,  $\beta$ ,  $\gamma$ ) has a specific influence on the stereochemical direction of organometallic synthesis. For this reason the rule of asymmetric induction [13],

which makes it possible to predict in advance the conformation of the predominant diastereoisomer in analogous reactions of carbonyl compounds of the aliphatic series, is not adequately trustworthy when applied to the stereoisomeric glycols (XII–XVI). In view of the fact that an effort to determine the mutual spatial distribution of the hydroxyl groups in these glycols by experiment failed to give positive results, the question of their conformation still remains unsolved. As a hypothesis, glycols (XII–XVI) are considered to belong to the series of erythro-isomers which, in accordance with the data in the literature [12], appears to be most probable.

TABLE 2. Stereoisomeric 1,2,5-Trimethyl-4-Hydroxy-4-Piperidylmethylarylcarbinols

No.	Ar	Isomer	M.p. or B.p.	Solvent for recrystallization	Yield %	Empirical formula	%N	
							found	calculated
(XII)	$C_6H_5$	$\alpha$	144–146° ch 221–222	ac	54	$C_{16}H_{25}O_2N$	5.39, 5.38	5.32
				ac + al	77	$C_{16}H_{26}O_2NCl$	4.39, 4.70	4.69
		$\beta$	hy 266–267	al		$C_{16}H_{26}O_2NCl$	4.76, 4.70	4.69
		$\gamma$	184–185 hy 255–256	b ac	85.9	$C_{16}H_{25}O_2N$	5.20, 4.89	5.32
(XIII)	$p\text{-CH}_3C_6H_4$	$\gamma$	86–86.5 hy 202–203	b ac + al	89	$C_{17}H_{27}O_2N$	5.12, 5.30	5.05
					—	$C_{17}H_{29}O_2NCl$	4.74, 4.85	4.46
(XIV)	$p\text{-(CH}_3)_2NC_6H_4$	$\gamma$	176.5–177 hy 191–192	ac ac + al	66	$C_{18}H_{30}O_2N_2$	8.93, 8.88	9.15
					—	$C_{18}H_{32}O_2N_2Cl_2$	7.47, 7.23	7.39
(XV)	$p\text{-CH}_3OC_6H_4$	$\alpha$	B.p. 140–145 (2 mm)		53	$C_{17}H_{27}O_3N$	4.56, 4.58	4.77
		$\beta$	hy 225–226	ac + al	85.4	$C_{17}H_{26}O_3NCl$	4.08, 4.07	4.24
		$\gamma$	hy 178–179	ac + al	75.1	$C_{17}H_{26}O_3NCl$	4.11, 4.19	4.24
(XVI)	$p\text{-C}_2H_5OC_6H_4$	$\alpha$	120–125 (2 mm)		56	$C_{18}H_{29}O_3N$	4.70, 4.58	4.53
		$\beta$	hy 197–198	ac	76.6	$C_{18}H_{30}O_3NCl$	4.05, 4.09	4.07
		$\gamma$	hy 188–189	ac	75.9	$C_{18}H_{30}O_3NCl$	4.37, 4.38	4.07

Note: b) Benzene, ac) acetone, al) alcohol, ch) chlorohydrate.

#### EXPERIMENTAL PART

**1,2,5-Trimethyl-4-hydroxy-4-piperidylphenylcarbinol (VI  $\gamma$ ).** 20.1 g of the finely pulverized  $\gamma$ -isomer of 1,2,5-trimethyl-4-carbomethoxy-4-piperidol (I $\gamma$ ), b.p. 118–119°, was added, with cooling, to an ether solution of phenyllithium (prepared from 47 g of bromobenzene and 4 g of lithium in 200 ml of ether) at such a rate that the ether boiled evenly. Then the reaction mixture was heated for four hours with the ether boiling moderately, after which it was cooled and hydrolyzed with 75 ml of water. The crystals that separated were filtered off, washed with water and dried in a vacuum-desiccator. 30.5 of glycol (VI $\gamma$ ) was obtained.

**1,2,5-Trimethyl-4-hydroxypiperidyl-di(p-methoxyphenyl)carbinol (X $\gamma$ ).** 20.1 g of the  $\gamma$ -isomer of 1,2,5-trimethyl-4-carbomethoxy-4-piperidol (I $\gamma$ ) was added to an ether solution of p-anisylmagnesium bromide prepared from 56 g of p-bromoanisole and 7.3 g of magnesium in 250 ml of ether. The reaction mixture was heated for four hours with the ether boiling moderately, and after cooling it was hydrolyzed with 150 ml of a saturated solution of ammonium chloride. The ether layer was separated and the aqueous layer saturated with potash and extracted with



ether. After drying the ether extract with calcined magnesium sulfate and removal of the solvent, an uncrystallizable oil was obtained which was converted into the hydrochloride. After recrystallization, 17.1 g of glycol (X $\gamma$ ) was obtained.

1,2,5-Trimethyl-4-hydroxy-4-piperidylmethylphenylcarbinol (XII $\gamma$ ). 18.5 g of the finely pulverized  $\gamma$ -isomer of 1,2,5-trimethyl-4-acetyl-4-piperidol (II $\gamma$ ), b.p. 59-60° was added in small portions, while the flask was cooled in ice water, to an ether solution of phenyllithium prepared from 62.8 g of bromobenzene and 5.5 g of lithium in 200 ml of absolute ether. The reaction mixture was heated for six hours with the ether boiling moderately, and then cooled and hydrolyzed with 100 ml of water. The crystals that separated were filtered off, washed twice on the filter with water, and dried in a vacuum-desiccator. 23.7 g of material was obtained. The aqueous layer was saturated with potash and extracted with ether. After removing the solvent from the ether extract, which was dried over magnesium sulfate, an additional 0.5 g of an oily substance was obtained which slowly crystallized and was found to be identical with the basic product. Altogether 24.2 g of glycol (XII $\gamma$ ) was obtained in the experiment.

1,2,5-Trimethyl-4-hydroxy-4-piperidylmethyl-(p-methoxyphenyl)carbinol (XV $\beta$ ). 18.5 g of the finely pulverized  $\beta$ -isomer of 1,2,5-trimethyl-4-acetyl-4-piperidol (II $\beta$ ), b.p. 129-130°, was added, while cooling with ice water, to an ether solution of p-anisylmagnesium bromide prepared from 48.7 g of p-bromoanisole and 6.5 g of magnesium shavings in 200 ml of absolute ether. After carrying out the reaction as described above for glycol (X $\gamma$ ), the reaction mixture was hydrolyzed with 150 ml of a saturated solution of ammonium chloride. The ether layer was separated, the aqueous layer saturated with potash and extracted with ether. After drying the combined ether extracts with calcined magnesium sulfate and removal of the solvent, an uncrystallizable base of glycol (XV $\beta$ ) was obtained which was converted into the hydrochloride. 22.4 g of the hydrochloride of glycol (XV $\beta$ ) was obtained.

#### SUMMARY

1. The reaction of geometric isomers of 1,2,5-trimethyl-4-carbomethoxy-4-piperidol and 1,2,5-trimethyl-4-acetyl-4-piperidol with organometallic compounds was studied. Stereoisomeric 1,2,5-trimethyl-4-hydroxy-4-piperidylmethylaryl- and 1,2,5-trimethyl-4-hydroxy-4-piperidyl-diarylcarbinols were obtained which are intermediates for the synthesis of potentially analgesic compounds—stereoisomeric analogs of ketobemidone.
2. The similarity of 1,2,5-trimethyl-4-hydroxy-4-piperidyl-diarylcarbinols and 1,2,5-trimethyl-4-hydroxy-4-piperidylmethylarylcarbinols to the pseudo-bases of dyes of the triphenylmethane series was demonstrated.
3. The stereochemical direction of the addition of organometallic compounds to the carbonyl group of the geometric isomers of 1,2,5-trimethyl-4-acetyl-4-piperidol was established. Each geometric isomer of this ketoalcohol forms one of two possible (erythro- and threo-) diastereoisomeric glycols.

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THE SYNTHESIS OF GEOMETRICAL ISOMERS  
OF 1,2,5-TRIMETHYL-4-ARYL-4-PIPERIDYLMETHYL-  
AND 1,2,5-TRIMETHYL-4-ARYL-4-PIPERIDYLARYLKETONES

B. V. Unkovskii and I. A. Mokhir

M. V. Lomonosov Moscow Institute of Fine Chemical Technology

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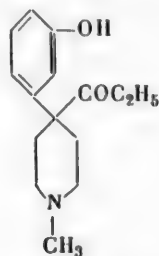
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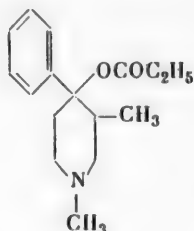
In a previous paper [1] we described various stereoisomeric piperidine  $\alpha$ -glycols that were prepared by the reaction of geometrical isomers of 1,2,5-trimethyl-4-carbomethoxy-4-piperidol [2, 3] and 1,2,5-trimethyl-4-acetyl-4-piperidol [3, 4] with organometallic compounds. In the present study, which was undertaken at the suggestion of I. N. Nazarov, stereoisomeric 1,2,5-trimethyl-4-aryl-4-piperidylmethyl- and 1,2,5-trimethyl-4-aryl-4-piperidyl-arylketones, formed by means of the pinacol-pinacolone rearrangement of these piperidine pinacols, are described. The ketones synthesized are the first representatives of previously unknown stereoisomeric analogs of 1-methyl-4-(*m*-hydroxyphenyl)-4-piperidylethylketone (ketobemidone) [5], one of the most active synthetic substitutes for morphine. Stereoisomeric compounds in the ketobemidone series and its analogs have been practically unavailable up to the present because of the absence of convenient and rational methods of preparing them.

Pharmacological experiments with stereoisomeric 1,2,5-trimethyl-4-aryl-4-piperidylmethyl- and 1,2,5-trimethyl-4-aryl-4-piperidylarylketones, which are potential analgesics, makes it possible to explain the dependence of the pain-relieving action of the geometrical isomers on their spatial structure, and may lead to the discovery of new products which do not have the disadvantage of ketobemidone.

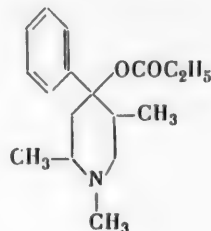
It is, moreover, extremely interesting to compare the pain-relieving activity of these ketones with the esters of the stereoisomeric 1,2,5-trimethyl-4-aryl-4-piperidols, previously studied in our laboratory, among which were found the valuable analgesics, promedol and isopromedol [6], which are stereoisomeric analogs of nisentil (prodine) [7].



Ketobemidone



Nisentil



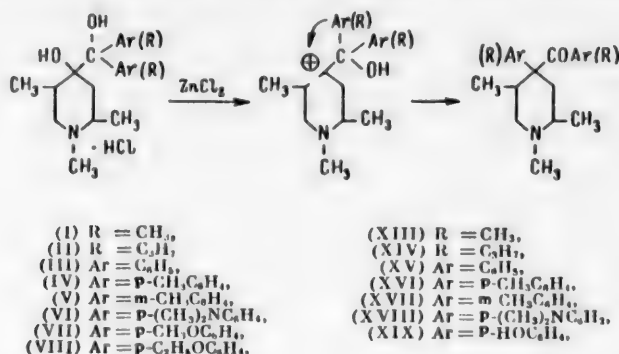
Promedol

As a method for preparing the geometric isomers of 1,2,5-trimethyl-4-aryl-4-piperidylmethyl- and 1,2,5-trimethyl-4-aryl-4-piperidylarylketones, we used the dehydration of the hydrochlorides of the corresponding stereoisomeric piperidine pinacols by means of Lewis acid—anhydrous zinc chloride in acetic anhydride [8].

Meerwin [9] was the first to discover that, depending on the reaction medium and the character of the water-removing agent, the dehydration of cyclic  $\alpha$ -glycols proceeds either with a rearrangement of the pinacol-pinacolone type or the formation of  $\alpha$ -oxides, or with an expansion of the ring. Nevertheless up to the present there has been extremely contradictory data from various authors [10-12] in regard to the direction of dehydration of cyclic  $\alpha$ -glycols, while not long ago [8, 13] it had still not been established that a rearrangement of the first type takes place by the action on pinacols of anhydrous zinc chloride in acetic anhydride, while expansion of the ring occurs preferentially

on dehydration by means of concentrated sulfuric acid. The stereoisomeric 1,2,5-trimethyl-4-hydroxy-4-piperidyl-diaryl- and 1,2,5-trimethyl-4-hydroxy-4-piperidyl-diarylcarbinols (I-VIII [1]) dehydrate, analogously to other cyclic  $\alpha$ -glycols in an energetic acetylating aprotic medium through the action of zinc chloride, exclusively in accordance with the pinacol-pinacolone rearrangement. The carbonium ion, which is initially formed as an intermediate structure, is stabilized by an anionic rearrangement with the migration of one of the radicals to the positively charged  $C_4$  of the piperidine ring, and by the formation of the corresponding geometrical isomer of 1,2,5-trimethyl-4-aryl-4-piperidylaryl- and 1,2,5-trimethyl-4-alkyl-4-piperidylalkylketones (XIII-XIX).

Under these conditions the hydrochlorides of the geometrical isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidyl-diphenylcarbinol (III $\alpha$ ,  $\beta$ ,  $\gamma$ ) are converted into stereoisomeric ketones, (XV $\alpha$ ,  $\beta$ ,  $\gamma$ ). In a similar way the pinacols (I), (II), (IV-VI) were converted into the corresponding geometrical isomers of ketones (XIII), (XIV) and (XVI-XVIII).



The infrared spectra of the ketones (XV) showed an intense vibrational frequency ( $1702\text{ cm}^{-1}$ ) which is characteristic of the carbonyl group, indicating that compounds (XIII-XIX) are indeed ketones and not oxides.

On dehydrating the hydrochlorides of  $\beta$ - and  $\gamma$ -isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidyl-di(p-methoxyphenyl)- and 1,2,5-trimethyl-4-hydroxy-4-piperidyl-di(p-ethoxyphenyl)-carbinols (VII $\beta$ ,  $\gamma$ ) and (VIII $\beta$ ,  $\gamma$ ), instead of the four stereoisomeric ketones expected, only two isomeric compounds were obtained, since, as a result of rearrangement, pinacols (VII $\beta$ ) and (VIII $\beta$ ) were converted into the same ketone (XIX $\beta$ ), while pinacols (VII $\gamma$ ) and (VIII $\gamma$ ) were converted into ketone (XIX $\gamma$ ). Samples of ketone (XIX $\beta$ ) obtained from (VII $\beta$ ) and (VIII $\beta$ ), as well as ketones (XIX $\gamma$ ) formed by pinacols (VII $\gamma$ ) and (VIII $\gamma$ ), were found to be identical and showed no depression of the temperature in a mixed melting point test. The anomalous character of the pinacol-pinacolone rearrangement of the stereoisomeric glycols (VII $\beta$ ,  $\gamma$ ) and (VIII $\beta$ ,  $\gamma$ ) gives evidence of the cleavage of the alkoxy groups, accompanying the dehydration, under the influence of Lewis acid, which is a new example of the rupture of ether bonds by metal chlorides [14].

Since it has been found that among the known analogs of ketobemidone, maximum analgesic activity occurs in compounds containing hydroxy groups in the aromatic ring, while the alkoxy compounds are usually inactive [5], it was indeed propitious that in our experiments the hydroxy compounds could be prepared directly by dehydration, thus avoiding the necessity of further cleavage of the alkoxy compounds by the Zeisel method.

The properties of the geometrical isomers of 1,2,5-trimethyl-4-aryl-4-piperidylaryl- and 1,2,5-trimethyl-4-alkyl-4-piperidylalkylketones (XIII-XIX) are shown in Table 1.

In connection with the fact that the pinacol-pinacolone rearrangement of pinacols (I-VIII) takes place with a rotation of the spatial configuration around the asymmetric  $C_4$  of the piperidine ring, and gives the synthesized geometrical isomers of ketones (XIII-XIX) the following spatial structure which is determined by the spatial configuration of the corresponding geometrical isomers of the original pinacols (I-VIII) [1]:

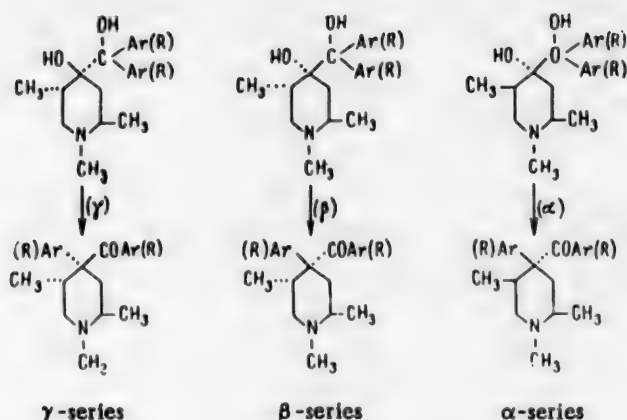


TABLE 1. Stereoisomeric 1,2,5-Trimethyl-4-Alkyl-4-Piperidylalkyl- and 1,2,5-Trimethyl-4-Aryl-4-Piperidylarylketones

$  \begin{array}{c}  (\text{Ar})\text{R} \quad \text{COR}(\text{Ar}) \\  \diagup \quad \diagdown \\  \text{CH}_3 \quad \text{CH}_3 \\  \diagdown \quad \diagup \\  \text{N} \quad \text{CH}_3 \\    \\  \text{CH}_3  \end{array}  \cdot \text{HCl}  $								
No.	R(Ar)	Iso-mer	M.p.	Solvent for re-crystall-ization	yield (in %)	Empirical formula	% N	
							Found	Calc.
(XIII)	CH <sub>3</sub>	γ	226—227°	ac	92.5	C <sub>11</sub> H <sub>22</sub> ONCl	6.26, 6.27	6.38
(XIV)	C <sub>3</sub> H <sub>7</sub>	γ	155—156	ac	85	C <sub>15</sub> H <sub>30</sub> ONCl	5.20, 5.22	5.08
(XV)	C <sub>6</sub> H <sub>5</sub>	α	297—298	ac + met	70.0	C <sub>21</sub> H <sub>26</sub> ONCl	4.05, 4.40	4.08
		β	257—258	ac	95	C <sub>21</sub> H <sub>26</sub> ONCl	4.37, 4.40	4.08
		γ	235.5—236	al	60	C <sub>21</sub> H <sub>26</sub> ONCl	4.05, 4.14	4.08
(XVI)	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	β	194—195	al	90	C <sub>23</sub> H <sub>30</sub> ONCl	3.79, 3.93	3.79
		γ	245—246	al + b	71.9	C <sub>23</sub> H <sub>30</sub> ONCl	3.77, 3.97	3.79
(XVII)	m-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	γ	220—221	ac	46.2	C <sub>23</sub> H <sub>30</sub> ONCl	3.58, 3.70	3.79
(XVIII)	p-(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> *	γ	244—245	al	71.1	C <sub>25</sub> H <sub>35</sub> ON <sub>3</sub>	10.66, 11.0	10.68
(XIX)	p-HOC <sub>6</sub> H <sub>4</sub>	β	176—177	ac	74.0	C <sub>21</sub> H <sub>26</sub> O <sub>2</sub> NCl	3.90, 3.91	3.74
		γ	247—248	al	70.7	C <sub>21</sub> H <sub>26</sub> O <sub>2</sub> NCl	3.73, 4.01	3.74

Note: ac) Acetone, al) alcohol, b) benzene, met) methanol.

In contrast to pinacols (I-VIII), the pinacol-pinacolone rearrangement of the geometrical isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethylarylcbinols (IX-XII) [1] may formally proceed by means of the migration of both alkyl and aromatic radicals and lead to the formation of the corresponding isomeric ketones. It has been shown by a number of studies [15], however, that in such cases it is precisely the aromatic radicals which migrate.

In the light of the most recent concepts [16] on the mechanism of the dehydration of α-glycols, the regularity of the preferential change in position of radicals is explained by their differing polarities, which may be expressed by the series of mobilities  $\text{Ar} > \text{C}_6\text{H}_5 > \text{H} > \text{R}$ .

\* Base.

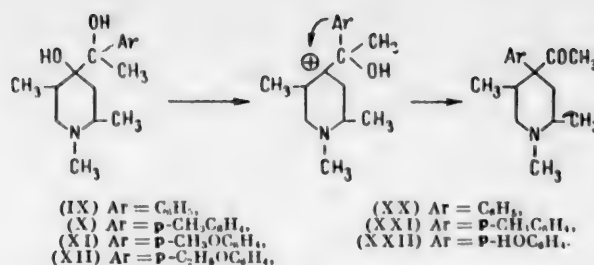


TABLE 2. Stereoisomeric 1,2,5-Trimethyl-4-Aryl-4-Piperidylmethylketones

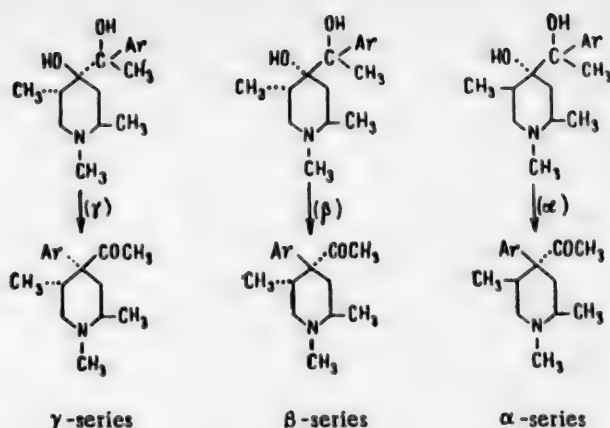
No.	Ar	Iso- mer	M.p.	Solvent for re- crystall- ization	yield (in %)	Empirical formula	% N	
							found	calc.
(XX)	C <sub>6</sub> H <sub>5</sub>	α	190—190.5°	ac	57	C <sub>16</sub> H <sub>24</sub> ONCl	4.86, 4.85	4.98
		β	140—141	ac	62.9	C <sub>16</sub> H <sub>24</sub> ONCl	4.65, 4.61	4.98
		γ	197—198	Dioxane	66.3	C <sub>16</sub> H <sub>24</sub> ONCl	4.88, 4.62	4.98
(XXI)	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	γ	106—107.5	ac	93.2	C <sub>17</sub> H <sub>26</sub> ONCl	4.63, 4.70	4.73
(XXII)	p-HOC <sub>6</sub> H <sub>4</sub>	α	203—204	ac	54	C <sub>16</sub> H <sub>24</sub> O <sub>2</sub> NCl	4.89, 4.78	4.73
		β	146—147	ac	94.5	C <sub>16</sub> H <sub>24</sub> O <sub>2</sub> NCl	4.90, 4.92	4.73
		γ	111—112	ac	86.6	C <sub>16</sub> H <sub>24</sub> O <sub>2</sub> NCl	4.89, 4.90	4.73

Note: ac) Acetone.

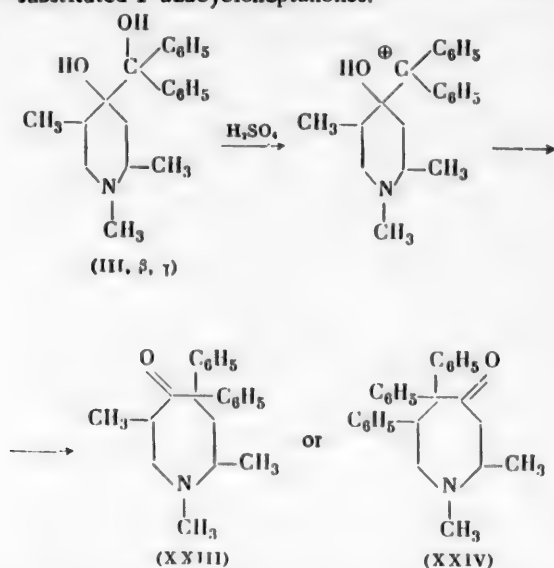
On dehydrating the chlorides of the geometrical isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethylphenylcarbinol (IXα, β, γ), we obtained diastereoisomeric 1,2,5-trimethyl-4-phenyl-4-piperidylmethylketones (XXα, β, γ). The infrared spectra of the stereoisomeric ketones (XX) showed an intense absorption peak at 1730 cm<sup>-1</sup> which is characteristic of the carbonyl group. Ketone (XXI) was prepared from glycol (X) in a similar manner. The dehydration of α, β, γ-isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-methoxyphenyl)-carbinol (XIα, β, γ) and of the corresponding geometrical isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-ethoxyphenyl)-carbinol (XIIα, β, γ), as a result of the cleavage of alkoxy groups as described above for carbinols (VIIβ, γ) and (VIIIβ, γ), leads to the formation of identical products for each geometrical isomer (XI) and (XII)—geometrical isomers of 1,2,5-trimethyl-4-(p-hydroxyphenyl)-4-piperidylmethylketone (XXIIα, β, γ) which are closest to ketobemidone in structure. The structure of the compounds obtained was confirmed by infrared spectra with intense absorption peaks at 1730 cm<sup>-1</sup> (carbonyl group) and 3520 cm<sup>-1</sup> (phenol hydroxyl).

The stereoisomeric α-phenylketones (XX-XXII), as well as ketones (XIII-XIX), are sterically hindered compounds. They do not show halochromism and, under ordinary conditions, do not form characteristic derivatives at the carbonyl group as was noted in the case of analogous compounds in the cyclohexane series [10]. The properties of ketones (XX-XXII) are shown in Table 2.

The spatial configuration of the stereoisomeric ketones (XX-XXII) is determined by the configuration of the corresponding geometrical isomers of the original pinacols (IX-XII) which we hypothetically assigned to the series of erythro-isomers [1]. The latter fact, however, is not of essential importance. In view of the possibility of the free rotation of the substituents at the carbinol carbon atom in the side chain, both the erythro- and the threo-isomers of the glycols (IX-XII) should give identical dehydration products since, according to the mechanism of pinacol-pinacolone rearrangement proposed by Zaleskaya [16], rotation in the cis-position of both hydroxyl groups with the formation of a ring complex creates the conditions of spatial equilibrium for the migrating radicals. In consideration of this, ketones (XX-XXII) have been assigned the following spatial configurations:



We also accomplished the dehydration of the  $\beta$ - and  $\gamma$ -isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidyl-diphenylcarbinol (III $\beta$ ,  $\gamma$ ) by means of concentrated sulfuric acid. Under these conditions, and contrary to the data in the literature [12], pinacols (III $\beta$ ,  $\gamma$ ) easily undergo rearrangement with expansion of the piperidine ring. The carbonium ion formed during dehydration in a proton medium is stabilized by the expansion of the piperidine ring with the formation of homopiperidones—substituted 1-azacycloheptanones.



It is interesting to note that the  $\beta$ - and  $\gamma$ -isomers of glycol (III), on dehydration by means of sulfuric acid, give identical products which show no depression in a mixed melting point test. In this case the pinacol-pinacolone rearrangement is accompanied by a disappearance of the asymmetric  $C_4$  of the piperidine ring in compounds (III $\beta$ ,  $\gamma$ ), which leads to the formation of one and the same product—1,2,6-trimethyl-4,4-diphenyl-1-azacycloheptane-5-one (XXIII) or 1,2,6-trimethyl-5,5-diphenyl-1-azacycloheptane-4-one (XXIV) which is isomeric with it. This observation is a supplementary confirmation of the conclusion we reached previously, namely, that in the series of derivatives of 1,2,5-trimethyl-4-piperidone, the steric isomers of the  $\beta$ - and  $\gamma$ -configurational series are epimers at the  $C_4$  of the piperidine ring and have an identical trans-diequatorial location of the methyl substituents [17]. Rearrangement of the glycols (III $\beta$ ,  $\gamma$ ) proceeds selectively and leads to the formation of one of the possible isomeric ketones (XXIII) or (XXIV); however no proof in favor of one structure or another is as yet available. The structure of the product obtained was confirmed by means of the UV spectrum, which showed the following absorption peaks ( $\lambda_{\max}$  259,  $\lg \epsilon$  3.0340;  $\lambda_{\max}$  265,  $\lg \epsilon$  2.9510;  $\lambda_{\max}$  295,  $\lg \epsilon$  2.860), which are characteristic of diphenylacetyl systems [18].

Compounds of the type of (XXIII) or (XXIV) are of pharmacological interest as starting materials for the synthesis of physiologically active compounds with the analgesic properties discovered in recent years among derivatives of 1-azacycloheptane [19]. The structural similarity of compound (XXIII) to the well-known analgesic phenadon (amidon) [20] is also of interest, since this ketone may be considered a cyclic analog of the latter.



The authors express their gratitude to Yu. G. Borod'ko and L. D. Miroshnichenko for taking and interpreting the infrared and UV spectra of the compounds mentioned.

#### EXPERIMENTAL PART

1,2,5-Trimethyl-4-phenyl-4-piperidylphenylketone (XVγ). A solution of 18 g of the hydrochloride of 1,2,5-trimethyl-4-hydroxy-4-piperidyl-diphenylcarbinol (IIIγ) with a m.p. of 236-237° [1] and 15 g of fused zinc chloride in 100 ml of acetic anhydride was stirred for two hours at 70-80°, after which it was diluted with 100 ml of water, neutralized with potassium carbonate and extracted with a mixture of ether and acetone. After drying the extract over calcined magnesium sulfate and removal of the solvent, the oily residue rapidly crystallized completely. After recrystallization 10.6 g of ketone (XVγ) was obtained.

1,2,5-Trimethyl-4-phenyl-4-piperidylmethylketone (XXγ). In accordance with the method described above, 6.15 g of ketone (XXγ), b.p. 165-170° (2 mm) was obtained from 10 g of the hydrochloride of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethylphenylcarbinol (IXγ), m.p. 255-256° [1] and 10 g of fused zinc chloride in 75 ml of acetic anhydride.

1,2,5-Trimethyl-4-(p-hydroxyphenyl)-4-piperidylmethylketone (XXIIα). a) 1.5 g of the hydrochloride of ketone (XXIIα) was obtained, as described above, from 3 g of the oily hydrochloride of the α-isomer of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-methoxyphenyl)-carbinol (XIα) and 3 g of fused zinc chloride in 30 ml of acetic anhydride.

b) 1.6 g (45%) of the hydrochloride of (XXIIα) was obtained from 3 g of the oily hydrochloride of the α-isomer of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-ethoxyphenyl)-carbinol (XIIα) and 3 g of fused zinc chloride in 30 ml of acetic anhydride. A mixed melting point test with a sample of the hydrochloride of ketone (XXIIα), prepared in the preceding experiment, showed no depression.

1,2,5-Trimethyl-4-(p-hydroxyphenyl)-4-piperidylmethylketone (XXIIβ). a) 14.5 g of the hydrochloride of ketone (XXIIβ) was obtained from 17 g of the hydrochloride of the β-isomer of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-methoxyphenyl)-carbinol (XIβ), m.p. 225-226°, and 15 g of fused zinc chloride in 100 ml of acetic anhydride.

b) 10 g (96.5%) of the hydrochloride of ketone (XXIIβ) was obtained from 11 g of the hydrochloride of the β-isomer of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-ethoxyphenyl)-carbinol (XIIβ), m.p. 197-198°, and 10 g of fused zinc chloride in 100 ml of acetic anhydride. A mixed melting point test with a sample of the hydrochloride of ketone (XXIIβ), obtained in the preceding experiment, showed no depression.

1,2,5-Trimethyl-4-(p-hydroxyphenyl)-4-piperidylmethylketone (XXIIγ). a) 10.7 g (86.6%) of the base of ketone (XXIIγ), b.p. 94-97° (0.1 mm) was obtained from 12 g of the hydrochloride of the γ-isomer of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-methoxyphenyl)-carbinol (XIγ), m.p. 178-179°, and 10 g of fused zinc chloride in 100 ml of acetic anhydride.

b) 12.6 g (85.3%) of the hydrochloride of ketone (XXIIγ) was obtained from 15 g of the hydrochloride of 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-ethoxyphenyl)-carbinol (XIIγ), m.p. 188-189°, and 12 g of fused zinc chloride in 100 ml of acetic anhydride. A mixed melting point test with a sample of the hydrochloride of ketone (XXIIγ), obtained in the preceding experiment, showed no depression.

1,2,6-Trimethyl-4,4-diphenyl-1-azacycloheptane-5-one (XXIII) or 1,2,6-trimethyl-5,5-diphenyl-1-azacycloheptane-4-one (XXIV). a) 7.7 g of the β-isomer of 1,2,5-trimethyl-4-hydroxy-4-piperidyl-diphenylcarbinol (IIIβ), m.p. 233-233.5° [1], was dissolved in 50 ml of concentrated sulfuric acid cooled by ice. After two hours the reaction mixture was poured into 100 ml of water, neutralized and saturated with potassium carbonate. The oily product that separated was extracted with ether. After drying the ether extract over calcined magnesium sulfate and removal of the solvent, an oily base was obtained which rapidly crystallized completely. After recrystallization 5.6 g (76%) of ketone (XXIII) or (XXIV), m.p. 112-113°, was obtained.

b) In a similar manner 5.2 g (83.5%) of ketone (XXIII) or (XXIV), m.p. 112-113° (after recrystallization) was obtained from 6.6 g of the γ-isomer of 1,2,5-trimethyl-4-hydroxy-4-piperidyl-diphenylcarbinol (IIIγ), m.p. 217-218° [1], and 35 ml of concentrated sulfuric acid. A mixed melting point test with a sample of ketone (XXIII) or (XXIV), obtained in the preceding experiment, showed no depression.

## SUMMARY

1. The dehydration of the stereoisomeric 1,2,5-trimethyl-4-hydroxy-4-piperidyldiaryl- and 1,2,5-trimethyl-4-hydroxy-piperidylmethylarylcarbinols by means of anhydrous zinc chloride in acetic anhydride was accomplished. As a result of the pinacol-pinacolone rearrangement of the stereoisomeric piperidine pinacols, the stereoisomeric 1,2,5-trimethyl-4-aryl-4-piperidyldiaryl- and 1,2,5-trimethyl-4-aryl-4-piperidylmethylketones were obtained. These compounds are the first representatives of previously unknown stereoisomeric analogs of the analgesic, ketobemidone.

2. It was shown that dehydration of the stereoisomeric 1,2,5-trimethyl-4-hydroxy-4-piperidyldi-(p-alkoxyphenyl)- and 1,2,5-trimethyl-4-hydroxy-4-piperidylmethyl-(p-alkoxyphenyl)-carbinols is accompanied by cleavage of the alkoxy groups and the formation of the corresponding geometrical isomers of 1,2,5-trimethyl-4-(p-hydroxyphenyl)-4-piperidyl-(p-hydroxyphenyl) and 1,2,5-trimethyl-4-(p-hydroxyphenyl)-4-piperidylmethylketones.

3. The dehydration of the  $\beta$ - and  $\gamma$ -isomers of 1,2,5-trimethyl-4-hydroxy-4-piperidyldiphenylcarbinol by means of concentrated sulfuric acid was accomplished. This led to the formation of homopiperidones. Both geometrical isomers formed identical products of dehydration—1,2,6-trimethyl-4,4-diphenyl-1-azacycloheptane-5-one or 1,2,6-trimethyl-5,5-diphenyl-1-azacycloheptane-4-one. This is a supplementary confirmation of the conclusion reached previously that in the series of derivatives of 1,2,5-trimethyl-4-piperidone, the geometrical isomers of the  $\beta$ - and  $\gamma$ -configurational series are epimers at the C<sub>4</sub> of the piperidine ring.

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# DERIVATIVES OF A VINYLENE HOMOLOG OF BENZOTRIFLUORIDE

L. M. Yagupol'skii and Yu. A. Fialkov

Institute of Organic Chemistry

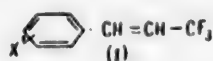
Academy of Sciences of the Ukrainian SSR

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 11,

pp. 3586-3593, November, 1961

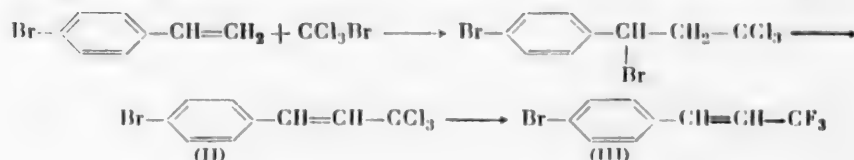
Original article submitted December 12, 1960

In a preceding paper the synthesis of 1-phenyl-2-trifluoromethylethylene (I)—a vinylene homolog of benzotrifluoride—was described [1]. It seemed of interest to prepare derivatives of compound (I) containing substituents, X, in the benzene ring, and to study the reciprocal influence of these substituents and the trifluoromethyl group.

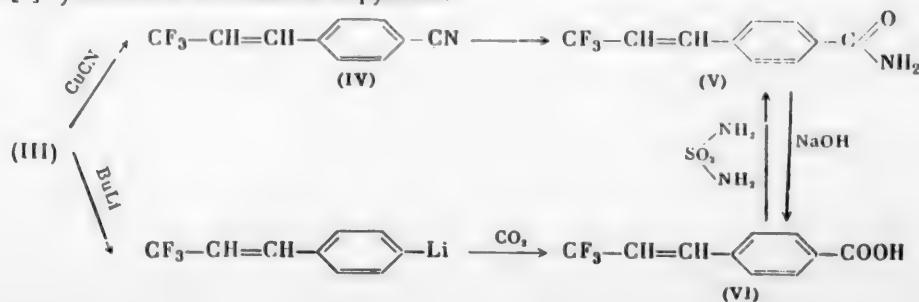


For the synthesis of para-derivatives of compound (I), the addition of bromotrichloromethane to various para-substituted styrenes was studied. The reaction was carried out by heating on a water bath with an excess of bromotrichloromethane in presence of benzoyl peroxide. Under these conditions p-nitro- and p-acetylaminostyrenes are converted into polymers but p-cyanostyrene does not react with bromotrichloromethane. On boiling p-nitrostyrene with an excess of bromotrichloromethane in a current of inert gas without benzoyl peroxide, which causes polymerization, the original material was recovered.

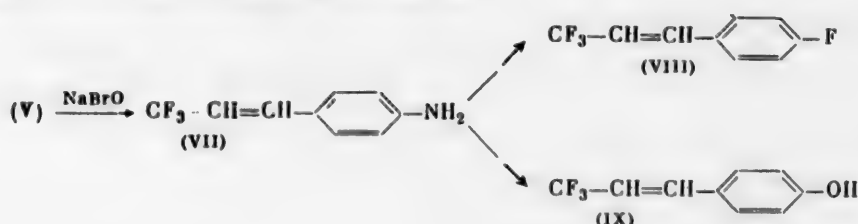
p-Bromostyrene adds bromotrichloromethane in the presence of benzoyl peroxide. The reaction gives off heat and 1-(p-bromo-phenyl)-1-bromo-3,3,3-trichloropropane is formed. From this, by splitting off hydrogen bromide by means of triethylamine, 1-(p-bromophenyl)-2-trichloromethylethylene (II) was obtained which, by fluorination with antimony trifluoride in dioxane, was converted into p-bromophenyltrifluoromethylethylene (III).



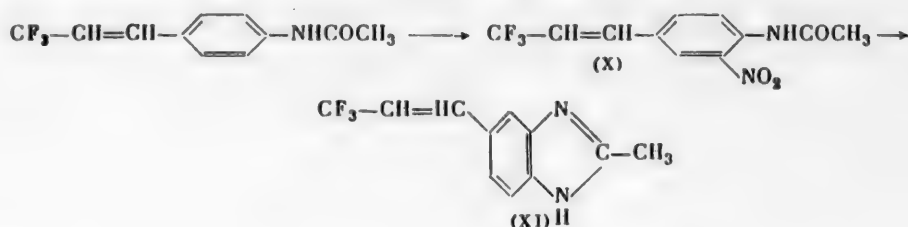
It proved impossible to obtain organomagnesium compounds from substance (III) and magnesium in ether. p-Bromophenyltrifluoromethylethylene, by heating with cuprous cyanide in pyridine, was converted into the nitrile (IV), from which, by the action of hydrogen peroxide in alkaline solution, the amide (V) was obtained. By hydrolyzing (V) by boiling with an aqueous solution of alkali, p-carboxyphenyltrifluoromethylethylene (VI) was formed. The latter was also synthesized by another method—by the metallation of p-bromophenyltrifluoromethylethylene by means of butyl lithium, with subsequent treatment of the lithium derivative with carbon dioxide. Acid (VI) was converted into the amide (V) [2] by the action of sulfamide in pyridine.



Amide (V), by means of the Hoffman method, was converted into amine (VII) from which p-fluoro-(VIII) and p-hydroxy-phenyltrifluoromethylethyls (IX) were obtained.



In order to prepare meta-derivatives of phenyltrifluoromethylethylene, p-acetylaminophenyltrifluoromethylethylene was nitrated; in this case the nitro group was in the ortho-position to the acetyl amino group, on reductive cyclization of the nitroacetyl amino compound (X), 2-methyl-5-(trifluoromethylvinyl)-benzimidazol (XI) was formed.



After saponification of the acetyl group in compound (X) and deamination, m-nitrophenyltrifluoromethylethylene was obtained. The latter was reduced to the amino compound, which was converted into m-hydroxyphenyltrifluoromethylethylene (XII).



The trifluoromethyl group in phenyltrifluoromethylethylene and its derivatives which contain electro-negative substituents, is stable in the presence of alkalis. Thus, after boiling phenyltrifluoromethylethylene with a 1 N aqueous solution of caustic soda for 1.5 hours, fluorine ions were not detected. 1-Phenyl-2-bromo-2-trifluoromethylethylene, on treatment with fused caustic potash at 230–250°, forms phenyltrifluoromethylacetylene in good yield [1]. The trifluoromethyl group is also not affected either when boiling amide (V) with a 10% aqueous solution of caustic soda for five hours for the purpose of preparing acid (VI), nor when heating nitrile (IV) with caustic soda in water-alcohol at 50° for one hour.

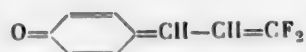
It has been mentioned in the literature that o- and p-hydroxybenzotrifluorides, unlike the meta-compounds, are not stable when treated with aqueous solutions of alkali [3]. It was of interest to investigate the behavior of the corresponding vinylene homologs of p- and m-hydroxybenzotrifluorides (IX and XII) under similar conditions.

The p-phenol (IX), on treatment with a 1 N solution of caustic soda for 30 minutes in the cold, was partially converted into a yellow amorphous substance. A large number of fluorine ions and some of the original phenol were found in the solution. The m-phenol (XI) does not split off fluorine ions under these conditions. Hydrolysis of the trifluoromethyl group in (IX) is considerably accelerated by heating.

By analogy with the polymer [3] prepared by the reaction of p-hydroxybenzotrifluoride with alkali, our yellow amorphous substance may have the structure



The fluorine content corresponds approximately with the formula indicated. Apparently, this compound is a linear polymer with a low degree of polymerization. The yellow color may be due to the presence of a colored monomer of quinoid structure



On boiling the p-phenol (IX) with 1 N caustic soda, the yellow substance that precipitates at first gradually goes into solution and within 1.5 hours has dissolved completely. After cooling, trans-p-hydroxycinnamic acid precipitates. The original phenol was not detected. It is interesting to note that the polymer obtained by the action of caustic soda on p-hydroxybenzotrifluoride, on longer boiling, does not split off fluorine even with a concentrated solution of caustic soda [3]. On boiling p-hydroxyphenyltrifluoromethylethylene with water (in a neutral medium) for 30 minutes, fluorine ions are not given off.

The m-phenol (XI) is considerably more stable in the presence of a boiling 1 N solution of caustic soda than the p-phenol. After heating for 1.5 hours, 85% of the unchanged substance was recovered. Fluorine ions were detected in the solution. m-Hydroxybenzotrifluoride is somewhat more stable in the presence of boiling alkali solutions than its vinyl homolog, since on boiling even with a 50% solution of caustic soda for 15 minutes, fluorine ions were not detected [3].

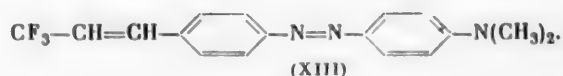
The trifluoromethyl group in the vinyl homolog of benzotrifluoride is considerably less stable in the presence of acids than in the presence of alkalies. Thus, phenyltrifluoromethylethylene, on heating with concentrated sulfuric acid, saponifies to cinnamic acid. This is decarboxylated, whereupon the styrene formed polymerizes [1]. On boiling p-bromophenyltrifluoromethylethylene with 55% sulfuric acid for two hours, fluorine ions were detected in the solution. In efforts to hydrolyze the nitrile (IV) to the amide (V) by means of concentrated sulfuric acid in the cold, and also the amide (V) to the acid (VI) by means of 45% sulfuric acid at 120° in the presence of sodium nitrite, saponification of the trifluoromethyl group occurs. In the latter case p-carboxycinnamic acid, b.p. 350° [4] was formed.

1-Phenyl-2-trifluoromethylethylene and its derivatives should be assigned to the trans-series. Thus, after fluorination of 1-phenyl-2-trichloromethylethylene and 1-(p-bromophenyl)-2-trichloromethylethylene, trans-cinnamic and trans-p-bromocinnamic acids were obtained. They were formed in consequence of the hydrolysis of the corresponding trichloromethyl derivatives as a result of the presence of traces of moisture in the reaction mixture. The trans-acid was also obtained by the hydrolysis of p-hydroxyphenyltrifluoromethylethylene.

The substituent  $\text{CF}_3-\text{CH}=\text{CH}$  differs sharply from the  $\text{CF}_3$  group in its influence on the benzene ring. Phenyltrifluoromethylethylene-p-carboxylic acid (VI) is considerably weaker than p-trifluoromethylbenzoic acid ( $\kappa \cdot 10^{-6}$  is 4.0 and 11.2 respectively). The  $\sigma$ -constants also differ sharply (for  $\text{CF}_3$  0.54, for  $\text{CF}_3-\text{CH}=\text{CH}$  0.23 [5]). By nitration of phenyltrifluoromethylethylene by means of nitric acid and oxidizing the mixtures of nitro products, approximately 50% of p-nitrobenzoic acid was obtained. Thus the  $\text{CF}_3-\text{CH}=\text{CH}$  group is a substituent of the first type (analogous to the  $\text{HOOC}-\text{CH}=\text{CH}$  group). It is known that benzotrifluoride nitrates 100% in the meta-position.

A study of the chemical displacement of the magnetic resonance of the  $\text{F}^{19}$  nuclei in fluorobenzenes with fluorine-containing substituents showed that the  $\text{CF}_3-\text{CH}=\text{CH}$  group has considerably less strength as an electron-acceptor than the  $\text{CF}_3$  group, and approaches halogen atoms in character [6].

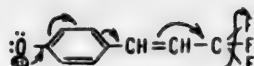
The azo dye (XIII) was also obtained



As was shown previously, the absorption peak of the salts of dimethylaminoazo compounds is more strongly displaced toward the long wave side than a more electro-positive substituent introduced into the para-position to the azo group [7]. In its influence on the color of salts of dimethylaminoazo compounds, the  $\text{CF}_3-\text{CH}=\text{CH}$  group approaches halogen atoms and differs from the  $\text{CF}_3$  group [7, 8].

Thus the vinyl group, located between the benzene ring and the trifluoromethyl group weakens the influence of the latter on the benzene ring to a considerable degree. At the same time the transfer of the electron action of the phenolate ion to the triphenylmethyl group through the vinyl group is easily accomplished.





## EXPERIMENTAL PART

**1-p-Bromophenyl-1-bromo-3,3,3-trichloropropene.** A mixture of 91.5 g of p-bromostyrene, 10 g of benzoyl peroxide and 450 g of bromotrichloromethane was stirred for six hours at 85°. When the reaction caused the flask to increase in temperature, it was cooled with water. Excess bromotrichloromethane was distilled off in the vacuum of a water pump. The yield was 105 g (55%). Needle-like crystals, m.p. 84.5-85.5° (from methanol).

Weighed sample 4.37 mg. Found, silver halide 9.34 mg.  $C_9H_7Cl_3Br_2$ -silver halide calculated 9.26 mg. Weighed sample 6.15 mg. Found, silver halide 13.26 mg. Silver halide calculated 13.02 mg.

**p-Bromophenyltrichloromethylethylene (II).** A mixture of 115 g of 1-p-bromophenyl-1-bromo-3,3,3-trichloropropene and 250 ml of triethylamine was stirred and boiled for six hours, then cooled and the crystals of the hydrobromide of triethylamine which had formed were filtered off. The crystals were washed twice on the filter with 30 ml of triethylamine each time, which was added to the basic filtrate. The triethylamine solution was poured, slowly and with cooling and stirring, into 1.5 liters of 10% sulfuric acid. An oil separated out and the remaining material was extracted twice with 300 ml of ether each time. The combined ether filtrates and the basic layer were washed twice with 300 ml of 10% sulfuric acid each time, then with a 5% solution of soda and water. After drying, the remaining material was distilled in vacuo. Yield 63 g (70%).

B.p. 120-121° (0.1 mm),  $n_D^{25}$  1.5974,  $d_4^{25}$  1.6416.

Weighed sample 5.65 mg. Found, silver halide 11.74 mg.  $C_9H_6Cl_3Br$ -silver halide calculated 11.61 mg. Weighed sample 5.37 mg. Found, silver halide 10.86 mg. Calculated silver halide 11.04 mg.

**p-Bromophenyltrifluoromethylethylene (III).** 60 g of antimony trifluoride and 240 ml of anhydrous dioxane were stirred together. 30-40 ml of dioxane was distilled off in order to remove moisture, the mixture was then cooled and 60 g of compound (II) added and boiled for seven hours. After cooling, the reaction mixture was treated with one liter of 20% hydrochloric acid and extracted twice with 300 ml of ether each time. The combined ether extracts were washed with 20% hydrochloric acid in order to remove antimony salts, then with water, a 5% solution of soda, again with water, and dried. On acidifying the soda washings trans-p-bromocinnamic acid, m.p. 255-256° [9], was obtained. The ether was distilled off and the remaining material distilled in vacuo. Yield 32.5 g (65%). B.p. 115° (25 mm), (760 mm, with partial decomposition). M.p. 21.5-22.5°.

Found %: Br 31.59, 31.68.  $C_9H_6F_3Br$ , calculated %: Br 31.83.

**p-Cyanophenyltrifluoromethylethylene (IV).** A mixture of 2.5 g of compound (III), 1.1 g of cuprous cyanide and 0.95 ml of pyridine was heated in a sealed ampoule for 16 hours at 200°. The contents of the ampoule were steam-distilled. Yield 1.05 g (53.5%). Needle-like crystals, m.p. 48-49.5° (from aqueous methanol).

Found %: N 7.11, 7.17.  $C_{10}H_6NF_3$ . Calculated %: N 7.10.

**p-Carboxyphenyltrifluoromethylethylene (VI).** a) From p-bromophenyltrifluoromethylethylene through the lithium derivative. In a three-necked flask which had been blown out with nitrogen in order to dry it and free it from oxygen, 35 g of (III) and 100 ml of absolute ether were placed. The solution was cooled to -30° and, while stirring, a solution of butyl lithium prepared from 3.5 g of lithium and 27.4 g of butyl bromide in 120 ml of ether was added through the dropping funnel. The addition was made at such a rate that the temperature in the flask did not rise above -30°. This required about one hour. The contents of the flask were then poured on 350 g of dry carbon dioxide. The mixture was stirred until it reached room temperature after which 300 ml of ether was added and the solution acidified with dilute hydrochloric acid until Congo showed an acid reaction. The ether solution was separated and the acid extracted by means of a 10% solution of caustic soda. The acid was precipitated by acidifying the alkaline extract with hydrochloric acid, filtered, washed with water and dried. The yield was 19.1 g (63%). Prism-like crystals, m.p. 247-248° (from methanol).

Found %: F 26.14; 26.55.  $C_{10}H_7O_2F_3$ . Calculated %: F 26.25.

b) **By alkaline hydrolysis of p-carbamidophenyltrifluoromethylethylene (V).** A mixture of 1 g of (V) and 5 ml of a 10% solution of caustic soda was boiled for five hours. It was then cooled, filtered from the insoluble residue and



acidified with hydrochloric acid. The acid that precipitated was then filtered off, washed with water and dried. The yield was 0.8 g (80%). M.p. 246-247°.

p-Carbamidophenyltrifluoromethylethylene (V). a) From p-cyanophenyltrifluoromethylethylene (IV). Four drops of 20% caustic soda were added to a mixture of 1.97 g of compound (IV), 15 ml of alcohol and 15 ml of 25% hydrogen peroxide. The mixture was gradually heated to 40-50°. After an hour the mixture was diluted with water and the crystals of the amide were filtered off, washed and dried. Yield 1.98 g (92%). Prism-like crystals, m.p. 189-190° (from ethanol).

Found %: N 6.63, 6.80.  $C_{10}H_8ONF_3$ . Calculated %: N 6.51.

b) From p-carboxyphenyltrifluoromethylethylene (VI). A mixture of 5.4 g of (VI), 4.8 g of sulfamide and 20 ml of pyridine was heated for three hours at 100°. The pyridine was distilled off in the vacuum of a water pump; the remaining material was suspended in water, the crystals of amide filtered off, washed with water and dried. Yield 4.7 g (87%). M.p. 188-190°.

p-Aminophenyltrifluoromethylethylene (VII). A solution of sodium hypobromite, prepared from 19 g of caustic soda in 160 ml of water and 4.8 ml of bromine, was added to 16.1 g of compound (V) in a flask equipped for steam distillation. The mixture was stirred for a few minutes while heating on a water bath and then the steam distillation was begun. The amine was filtered off and dried. The yield was 8.1 g (58%). Prism-like crystals, m.p. 82-83° (from petroleum ether).

Found %: N 7.44, 7.59.  $C_9H_8NF_3$ . Calculated %: N 7.48.

The acetyl derivative had a m.p. of 203-205° (from aqueous alcohol).

Found %: N 6.31, 6.34.  $C_{11}H_{10}NF_3$ . Calculated %: N 6.12.

p-Fluorophenyltrifluoromethylethylene (VIII). A suspension of 3.2 g of amine (VII) in 13 ml of 20% hydrochloric acid was diazotized by a solution of 1.15 g of sodium nitrate in 5 ml of water. The solution was filtered and at 0°, with stirring, a solution of 3.8 g of sodium borofluoride in 7 ml of water was added. This was stirred for five minutes, cooled to -10°, the crystals of diazonium borofluoride were filtered off and dried. Yield -3.2 g (66%). Decomposition temperature 143°. The diazonium borofluoride was placed in a long-necked flask with a reflux condenser and equipped for steam distillation, and decomposed by heating with the flame of a burner. After completion of the reaction the p-fluorophenyltrifluoromethylethylene was distilled off with steam, the distillate was extracted with ether, washed with a 5% solution of caustic soda, water and then dried. After removal of the ether the remaining material was distilled. Yield -1.3 g (40%, calculated on the p-aminophenyltrifluoromethylethylene). B.p. 165-166°,  $n_D^{20}$  1.4625,  $d_4^{20}$  1.2682.

Found %: C 56.54, 56.76; H 3.03, 3.12.  $C_9H_6F_4$ . Calculated %: C 56.84; H 3.18.

4-Dimethylamino-4'-3',3',3'-trifluoropropenyl-1'-azobenzene (XIII). A suspension of 9.15 g of p-aminophenyltrifluoromethylethylene in 8 ml of 24% hydrochloric acid was diazotized by a solution of 0.06 g of sodium nitrate in 1.5 ml of water. After diazotization this was stirred for ten minutes, then some crystals of urea were added to remove nitrogen oxides and the hydrochloric acid neutralized by means of sodium acetate. A solution of 0.12 g of dimethylaniline in 2 ml of 50% acetic acid was added to the filtered solution of the diazocompound at 0°; it was then stirred and allowed to stand over night. The crystals of dye which were formed were filtered off and washed with water. Platelets, m.p. 196-198° (from methanol).  $\lambda_{max}$  435m $\mu$  (in alcohol) and 536m $\mu$  (in alcohol-hydrochloric acid solution: Two volumes of alcohol per volume of hydrochloric acid (d 1.19).

Found %: N 12.96, 13.05.  $C_{17}H_{16}N_2F_3$ . Calculated %: N 13.16.

4-Acetyl-amino-3-nitrophenyltrifluoromethylethylene (X). A nitrating mixture prepared from 4 ml of 93% sulfuric acid and 4 ml of 70% nitric acid which had been cooled to -7°, was added drop by drop to 1.72 g of carefully pulverized p-acetylaminophenyltrifluoromethylethylene at from -5 to -7°. After all of the nitrating mixture had been added the reaction mixture was stirred for 2.5 hours at -2°. It was then poured over ice, the nitro product filtered off and washed until it ceased to give an acid reaction to Congo. Yellow needles, m.p. 169-170° (from aqueous alcohol). The yield was 1.33 g (65%).

Found %: N 10.18, 10.28.  $C_{11}H_9O_3N_2F_3$ . Calculated %: N 10.22.

2-Methyl-5-(trifluoromethylvinyl)-benzimidazol (XI). A mixture of 0.63 g of 4-acetyl-amino-3-nitrophenyltrifluoromethylethylene, 2.6 g of tin dichloride, 3 ml of concentrated hydrochloric acid and 3 ml of glacial acetic

acid was boiled for two hours. This was then cooled, a 20% solution of caustic soda added until it was strongly alkaline to phenolphthalein, and extracted with ether. The ether was distilled off, the remaining material dissolved in 10% hydrochloric acid, treated with activated carbon, filtered, and precipitated with a solution of ammonia. The precipitate was filtered off and crystallized from aqueous methanol containing activated carbon. The yield was 0.12 g (23%). M.p. 208-209°.

Found %: N 12.17, 12.19.  $C_{11}H_9N_2F_3$ . Calculated %: N 12.39.

4-Amino-3-nitrophenyltrifluoromethylethylene. A mixture of 1.76 g of compound (X), 1 ml of water, 3.6 ml of alcohol and 0.4 g of caustic potash was heated for 20 minutes on a boiling water bath. This was then cooled, diluted with water, the precipitate filtered off and washed with water. The yield was 1.4 g (94%). Orange-red needles, m.p. 120-121° (from aqueous alcohol).

Found %: N 12.14, 12.29.  $C_9H_7O_2N_2F_3$ . Calculated %: N 12.07.

m-Nitrophenyltrifluoromethylethylene. A solution of 0.4 g of sodium nitrite in 0.6 ml of water was added, at 0°, to a mixture of 1.06 g of 4-amino-3-nitrophenyltrifluoromethylethylene with 3 ml of alcohol and 0.7 ml of concentrated sulfuric acid. This was stirred for 20 minutes at 0° and then boiled for 2.5 hours. m-Nitrophenyltrifluoromethylethylene was distilled off with steam, the distillate was extracted with ether and the ether solution washed with a 1% solution of caustic soda, water and then dried. The ether was distilled off. The yield was 0.6 g (60%); m.p. 42.5-43.5° (from aqueous alcohol).

Found %: N 6.12, 6.27.  $C_9H_6O_2NF_3$ . Calculated %: N 6.45.

m-Aminophenyltrifluoromethylethylene. 0.65 g of m-nitrophenyltrifluoromethylethylene was dissolved in 30 ml of alcohol, 0.01 g of platinum black added and hydrogenated by agitating with hydrogen at atmospheric pressure and room temperature. The calculated quantity of hydrogen was absorbed in 45 minutes. The catalyst was filtered off and the solvent distilled off in the vacuum of a water pump. The yield was 0.55 g (98%). M.p. 29.5° (from petroleum ether, b.p. 40-50°).

Found %: N 7.34, 7.42.  $C_9H_8NF_3$ . Calculated %: N 7.48.

Acetyl derivative—needle-like crystals, m.p. 107.5-108.5° (from a mixture of petroleum ether and benzene).

Found %: N 6.11, 6.12.  $C_{11}H_{10}ONF_3$ . Calculated %: N 6.12.

p-Hydroxyphenyltrifluoromethylethylene (IX). 0.93 g of compound (VII) was suspended in a mixture of 1.5 ml of concentrated sulfuric acid and 10 ml of water and diazotized by a solution of 0.4 g of sodium nitrite in 1.5 ml of water at 2°. This was stirred for 35 minutes, the solution of the diazo compound filtered and then added drop by drop to a flask to be steam-distilled. The phenol was distilled off, the distillate cooled and the precipitate filtered off. The yield was 0.5 g (54%). Needle-like crystals, m.p. 71.5-72.5° (from petroleum ether, b.p. 50-60°). It sublimes easily.

Found %: F 30.17, 30.33.  $C_9H_7OF_3$ . Calculated %: F 30.29.

m-Hydroxyphenyltrifluoromethylethylene (XII). This was obtained in a similar manner from m-aminophenyltrifluoromethylethylene. B.p. 86° (0.2 mm). Yield 54%.

3,5-Dinitrobenzene derivative—needle-like crystals, m.p. 129-131° (from alcohol).

Found %: N 7.16, 7.26.  $C_{16}H_9O_6N_2F_3$ . Calculated %: N 7.34.

The reactions of p- and m-hydroxyphenyltrifluoromethylethylenes with a solution of caustic soda. a) 0.49 g of p-hydroxyphenyltrifluoromethylethylene was dissolved in 7.5 ml of 1 N caustic soda. The solution, which was colorless and transparent at first, became cloudy and turned yellow. It was heated for five minutes up to 75°. It was then cooled, the yellow amorphous precipitate filtered off, washed with water and dried over phosphorus pentoxide. The yield was 0.35 g (80%). M.p. 95-115°.

It was easily soluble in benzene, ether, methanol, slightly soluble in petroleum ether and insoluble in water.

Found %: F 21.26, 21.35. M 680 (cryoscopy in benzene).  $(C_9H_5OF_2)_x$ . Calculated %: F 22.60.

b) 0.1 g of p-hydroxyphenyltrifluoromethylethylene was dissolved in 4 ml of 1 N caustic soda and boiled for 1.5 hours. It was filtered free of turbidity and acidified with concentrated hydrochloric acid. The yield was 0.07 g (80%). M.p. 215-217° (decomp) which corresponds with trans-parahydroxycinnamic acid [10].

c) 0.4 g of m-hydroxyphenyltrifluoromethylethylene was dissolved in 6 ml of 1 N caustic soda and boiled for 1.5 hours. It was then cooled, acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was washed with water and dried. After removal of the ether, 0.34 g of the phenol was obtained. Its dinitrobenzene derivative did not show a depression in a mixed melting point test with a known sample.

#### SUMMARY

1. It was shown that p-nitro-, p-acetylamino-, and p-cyanostyrenes do not add bromotrichloromethane in the presence of benzoyl peroxide. p-Bromostyrene easily adds bromotrichloromethane. p-Bromo, p-cyano-, p-carboxy-, p-amino-, p-fluoro-, p-hydroxy- and m-nitro-, m-amino-, and m-hydroxy derivatives of 1-phenyl-2-trifluoromethylethylene were synthesized from this addition product.

2. The trifluoromethyl group in derivatives of the vinylene homolog of benzotrifluoride is more stable in the presence of acid reagents. The p-hydroxy-substituted derivative is an exception; in contrast to the m-hydroxy-compound it easily splits off hydrogen fluoride in the presence of alkaline reagents.

3. These derivatives of 1-phenyl-2-trifluoromethylethylene are assigned to the trans-series, since on hydrolysis they give the corresponding trans-cinnamic acids.

4. The trifluoromethylvinyl group is a substituent of the first order. The vinyl group, located between the benzene ring and the trifluoromethyl group, considerably weakens the electron-acceptor influence of the latter on the benzene group.

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# PHOSPHORYLATED CHLOROVINYLKETONES

## V. THE MECHANISM OF THE REARRANGEMENT OF THE ADDITION PRODUCTS OF PHOSPHORUS PENTACHLORIDE AND ESTERS OF ENOLS TO FORM PHOSPHORYLATED CHLOROKETONES

I. F. Lutsenko and M. Kirilov

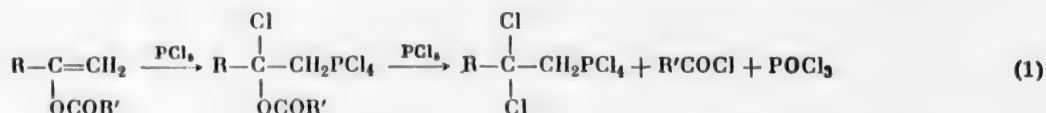
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 11,

pp. 3594-3601, November, 1961

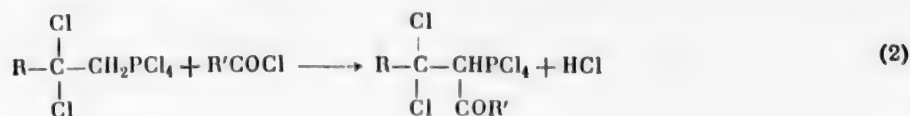
Original article submitted December 6, 1960

In previous papers [1-4] we have described the addition reaction of phosphorus pentachloride and esters of enols in carbon tetrachloride. It was shown that this is a two-stage reaction; the first stage is the addition of phosphorus pentachloride at a double bond—the carbon bond of the unsaturated ester, and at low temperatures the reaction may stop at this stage [2-4]. If, however, the reaction mixture containing the addition products is heated, or if the reaction is heated from the beginning [1, 3], then, after the addition of the phosphorus pentachloride at the double bond, the ester group also takes part in the reaction, as a result of which saturated and unsaturated phosphorylated chloroketones are obtained.

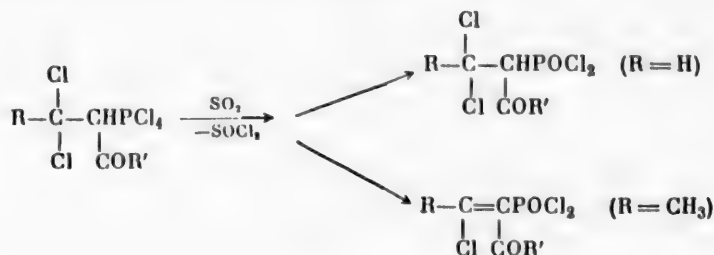
The following scheme was first suggested in order to explain the formation of these compounds:



It was assumed that the chloride of the carboxylic acid formed, acetylates the organophosphorus compound:



After treating the reaction mixture with sulfur dioxide the chlorides of phosphinic acids were obtained by distillation in vacuo.

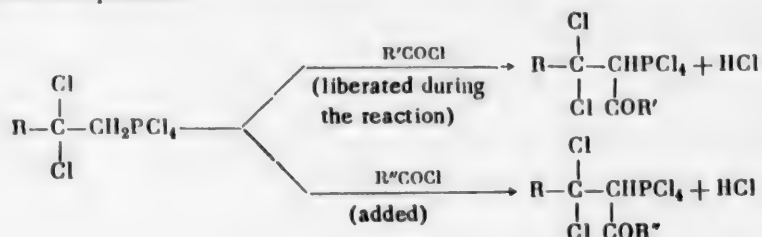


Further studies, however, failed to confirm this set of reactions; we reached this conclusion on the basis of the following facts.

1. In accordance with equation (2) one would expect that addition of acyl chloride to the reaction mixture would increase the yield of the end product (especially in the case where  $\text{R} = \text{CH}_3$ , where the yields are lower). As

a matter of fact, however, the yield of the chloride of  $\alpha$ -acetyl- $\beta$ -chloropropenylphosphinic acid (from isopropenylacetate and phosphorus pentachloride), in the presence of specially added acyl chloride, was no higher than in the control experiment (in the absence of acyl chloride).

2. If the reaction proceeds as indicated in equation (2), then the addition to the reaction mixture of the chloride of a carboxylic acid with an acyl residue differing from the acyl residue of the original ester, should result in the formation of mixed reaction products.



As a matter of fact, experiment showed that isopropenyl acetate reacts with phosphorus pentachloride in the presence of butyryl chloride, giving only the chloride of  $\alpha$ -acetyl- $\beta$ -chloropropenylphosphinic acid with a yield of 70%; the added butyryl chloride does not take part in the reaction.

In exactly the same way isopropenyl butyrate reacts with phosphorus pentachloride in the presence of acetyl chloride to give only the chloride of  $\alpha$ -butyryl- $\beta$ -chloropropenylphosphinic acid; and in this case the specially added acetyl chloride does not take part in the reaction.

On the basis of the facts given above, one may conclude that acyl chloride is not formed in the free state during the reaction, and that the reaction apparently proceeds by an intra-molecular mechanism.

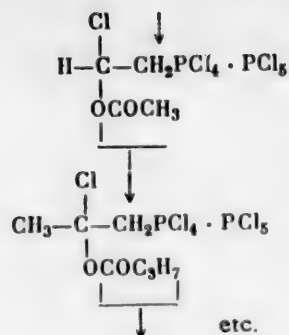
3. The results we obtained in our study of the reaction of phosphorus pentachloride with a mixture of vinyl acetate and isopropenyl butyrate agree with the hypothesis regarding the intra-molecular rearrangement of the primary addition products of phosphorus pentachloride and esters of enols into phosphorylated chloroketones.

In view of the fact that the optimum conditions for the reaction of phosphorus pentachloride with vinyl acetate and isopropenyl butyrate are different (about 40° and 50-70°, respectively [1]) the reaction was carried out twice: In one case at 40-45°, and in the other at 55-70°. In the experiment at 40-45° the chloride of  $\alpha$ -acetyl- $\beta$ , $\beta$ -dichloroethylphosphinic acid was separated from the reaction mixture in high yield—70% (from vinyl acetate only the yield was 85%); at the same time the chloride of  $\alpha$ -butyryl- $\beta$ -chloropropenylphosphinic acid was obtained in low yield (16%). In the experiment at 55-70° the latter was separated from the reaction mixture with a yield of 33% (from isopropenyl butyrate only the yield was 58%) while the chloride of  $\alpha$ -acetyl- $\beta$ , $\beta$ -dichloroethylphosphinic acid was obtained with a yield of 65% (in impure form, since the reaction was not carried out under the optimum conditions for producing it).

Thus, on carrying out the reaction of phosphorus pentachloride with a mixture of two esters of enols, only two reaction products are obtained—the chloride of  $\alpha$ -acetyl- $\beta$ , $\beta$ -dichloroethylphosphinic and the chloride of  $\alpha$ -butyryl- $\beta$ -chloropropenylphosphinic acids which correspond with the original enol esters.

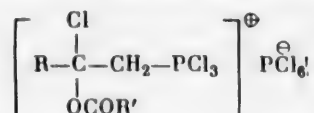
If the reaction scheme originally proposed were correct, two acyl halides would have been formed as intermediates, which would have resulted in the formation of the chlorides of four phosphinic acids. This was not confirmed by experiment, however. This permits us to draw the conclusion that the rearrangement of the addition products first formed, which results in the formation of phosphorylated chloroketones, is not connected with the formation of acyl halides (acyl cations respectively) as kinetically independent molecules and proceeds by an intra-molecular mechanism.

The results obtained also exclude such a formation of phosphorylated chloroketones when the reaction proceeds by "transfer" of the acyl radical from one molecule of the addition product to another.



If the reaction proceeded in this way, a mixture of four phosphorus-containing compounds would be obtained which, as a matter of fact, is not observed. On the basis of the above discussion it may be assumed that the formation of phosphorylated chloroketones is the result of an intra-molecular rearrangement of the addition products of phosphorus pentachloride to enol esters, with the transfer of an acyl group from an oxygen atom to a carbon atom that is linked with phosphorus (the  $\alpha$ -carbon atom).

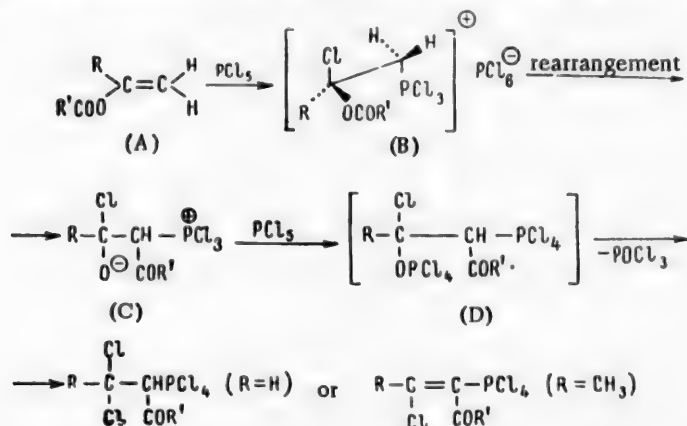
The ease with which a proton may be detached from an  $\alpha$ -carbon atom is of essential importance for this rearrangement. The large positive charge on the phosphorus atom linked to carbon must facilitate this detachment. This is possible if the addition product has a complex structure (its composition was demonstrated by us previously [2]).



As a matter of fact, after the disintegration of the complex by means of sulfur dioxide and its conversion into the chloride of  $\beta$ -acyloxy- $\beta$ -chloroalkylphosphinic acid, the rearrangement cannot be accomplished even in the presence of phosphorus pentachloride. Thus, the chloride of  $\beta$ -acetoxy- $\beta$ -chloroethylphosphinic acid does not rearrange in the presence of  $\text{PCl}_5$  even when heated for an hour at  $75-80^\circ$  and is recovered quantitatively. This fact indicates the decisive influence of the  $\alpha$ -hydrogen atom: the chloride of  $\beta$ -acetoxy- $\beta$ -chloroethylphosphinic acid does not rearrange because of the insufficient mobility of its hydrogen atom. The slight solubility of the reaction products in carbon tetrachloride gives some indirect evidence of their complex structure.

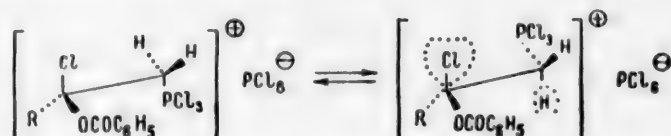
It should be noted that in the literature there are some indications of the existence of cations of the type  $[\text{RPCl}_3]^+$  [5]. The existence of a  $\text{PCl}_6^-$  anion in crystalline phosphorus pentachloride [6], and also in solutions of it in benzene and acetonitrile has been demonstrated [7]. If one accepts such a complex structure of the addition product (B), then the detachment of a proton from the  $\alpha$ -carbon atom should be accomplished by means of a  $\text{PCl}_6^-$  anion (forming the unstable acid  $\text{HPCl}_6$  which decomposes into  $\text{HCl}$  and  $\text{PCl}_5$ ).

The detachment of a proton is facilitated by the simultaneous approach of an acyl group located in the transposition to it. After its transfer the bipolar ion (C) is formed which reacts with  $\text{PCl}_5$ , giving an intermediate compound of the type  $\text{ROPCL}_4$  (D) which decomposes, liberating  $\text{POCl}_3$ , or, if  $\text{R} = \text{CH}_3$ , liberating  $\text{POCl}_3$  and  $\text{HCl}$  [8] as shown in the following scheme:



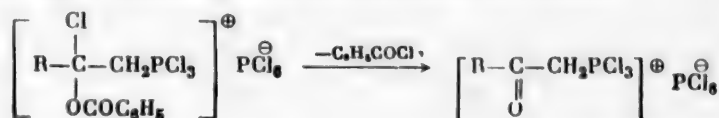


This proposed scheme for the mechanism of the reaction of phosphorus pentachloride with enol esters agrees well with the intra-molecular character of this reaction which we have demonstrated. The fact that isopropenylbenzoate does not give a rearranged product on reacting with phosphorus pentachloride, as we have reported [4], but instead splits off hydrogen chloride, while the addition product of phosphorus pentachloride with vinyl benzoate does rearrange, although with difficulty, (yield 35%), is apparently to be explained by the conformation of the products formed by the reaction of enol benzoates with phosphorus pentachloride. Because of the large size of the benzoyl-hydroxy group, its location in the *cis*-position to the  $\text{PCl}_3$  group which is also large, is hindered; the conformation with these groups in the *trans*-position is more favorable.

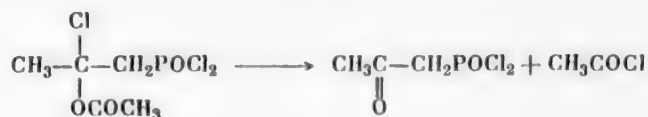


In this case, however, the mobile hydrogen atom changes position and rearrangement is hindered. The *trans*-elimination of hydrogen chloride is more probable. In the case of the addition product with vinyl benzoate ( $\text{R} = \text{H}$ ), the mobility of the chlorine atom is small and hence  $\text{HCl}$  is not split off and rearrangement occurs (although with difficulty).

In the case of the addition product with isopropenylbenzoate ( $\text{R} = \text{CH}_3$ ), cleavage occurs more easily than rearrangement. In both cases, because of difficulty in rearrangement and in cleavage of hydrogen chloride, side reactions occur to a considerable degree, apparently due to the cleavage of acyl chloride



similar to the way in which acetyl chloride splits off from the chloride of  $\beta$ -acetoxy- $\beta$ -chloropropylphosphinic acid [2].



In the first case, however, the exposed carbonyl group reacts further with phosphorus pentachloride freed from the complex, giving a mixture of low-boiling phosphorus-containing compounds (this mixture has not yet been studied). A similar side reaction apparently also takes place in the reaction of phosphorus pentachloride with the isopropenyl esters of aliphatic carboxylic acids, although to a considerably lesser degree than might be explained by the lower yields of the chlorides of  $\alpha$ -acyl- $\beta$ -chloropropenylphosphinic acids (58-77%) in comparison with the yields of the products of the vinyl esters of carboxylic acids—the chlorides of  $\alpha$ -acyl- $\beta$ , $\beta$ -dichloroethylphosphinic acids (85-90%).

It must be emphasized that the rearrangement of the addition products of phosphorus pentachloride with enol esters is an irreversible process since right after it substitution of an oxygen atom by chlorine occurs. This assures comparatively rapid rearrangement and high yields of the products of rearrangement, especially in the case of the vinyl esters of aliphatic carboxylic acids.

Increasing the temperature favors rearrangement (its rate increases faster than the rate of side reactions). This is evident in the case of the reaction of phosphorus pentachloride with isopropenyl acetate. At a temperature of 50-70°, the yield of the end product—the chloride of  $\alpha$ -acetyl- $\beta$ -chloropropenylphosphinic acid amounts to 70%, while when the reaction is carried out at 20°, the yield declines to 52%. However, increasing the temperature is limited by the fact that at high temperatures chlorination begins and in consequence the reaction products are contaminated by substances with closely-similar boiling points and cannot be purified by simple distillation.

## EXPERIMENTAL PART

### A. Preparation and rearrangement of the reaction product from vinyl acetate $[\text{CH}_3\text{COOCH}(\text{Cl})\text{CH}_2\text{PCl}_2]\text{PCl}_6$

The addition product is obtained by stirring a filtered solution of 41.6 g phosphorus pentachloride in 250 ml of carbon tetrachloride, and 8.6 g of vinyl acetate for six hours at a temperature of 7-8°, in accordance with the method described by us previously [2]. A small part of it was filtered off, washed with cold carbon tetrachloride, then with isopentane, and analyzed immediately.

Found %: C 9.22, 9.90; H 1.16, 1.65; P 12.25, 12.29.  $\text{C}_4\text{H}_6\text{O}_2\text{Cl}_3\text{P}_2$ . Calculated %: C 9.56; H 1.20; P 12.22.

The remainder of the reaction mixture was heated for two hours at 40°, cooled, treated with sulfur dioxide, the solvent, thionyl chloride and phosphorus oxychloride distilled off and the residue distilled in vacuo. 18.8 g (73%, not counting the material used for analysis) of the chloride of  $\alpha$ -acetyl- $\beta$ , $\beta$ -dichloroethylphosphinic acid was obtained. B.p. 98-99° (2.5 mm),  $n_D^{20}$  1.5098,  $d_4^{20}$  1.5460. For the data in the literature see [1].

B. The reaction of  $\text{PCl}_5$  with isopropenyl acetate at 20°. 30 g of isopropenyl acetate was added drop by drop, with stirring, to a suspension of 124.8 g of phosphorus pentachloride in 150 ml of carbon tetrachloride. Stirring was continued at 20° for another four hours, then sulfur dioxide was passed in. The solvent, thionyl chloride and phosphorus oxychloride were distilled off in vacuo, and then the remaining material was distilled. At first the fraction boiling at 95-115° (5 mm) (7.2 g, 23% of the total weight of the reaction products) was collected. Then the chloride of  $\alpha$ -acetyl- $\beta$ -chloropropenylphosphinic acid was distilled twice. Yield 24 g (52%) B.p. 118-120° (2.5 mm),  $n_D^{20}$  1.5240.

C. Reactions in the presence of acyl chlorides. 1. The reaction of phosphorus pentachloride with isopropenyl acetate in the presence of acetyl chloride. 20 g of isopropenyl acetate was added drop by drop, with stirring and cooling to -25°, to a filtered solution of 83.2 g of phosphorus pentachloride in 650 ml of carbon tetrachloride. This was stirred at the same temperature for another half hour; then 16 g of acetyl chloride was added and the mixture heated for one hour at 50-55° and one hour at 65-70°. After cooling, sulfur dioxide was passed through, the solvent, thionyl chloride and phosphorus oxychloride were distilled off in vacuo and the residue distilled. The fraction boiling between 116-120° (2 mm),  $n_D^{20}$  1.5235, was collected. The yield of the chloride of  $\alpha$ -acetyl- $\beta$ -chloropropenylphosphinic acid was 30.5 g (65%). A parallel experiment without the addition of acetyl chloride gave the same product ( $n_D^{20}$  1.5235) with a yield of 32.5 g (69.1%).

2. The reaction of phosphorus pentachloride with isopropenylacetate in the presence of butyryl chloride. 20 g of isopropenylacetate was added drop by drop, with stirring, to a suspension of 83.2 g of phosphorus pentachloride in 100 ml of butyryl chloride which had been heated to 50-55°. It was heated for a further two hours at 65-70°, cooled, and treated with sulfur dioxide. Then the solvent, thionyl chloride and phosphorus oxychloride were distilled off in vacuo, and the remaining material distilled. The fraction boiling at 118-122° (3 mm) was collected. The yield of the chloride of  $\alpha$ -acetyl- $\beta$ -chloropropenylphosphinic acid was 33 g (70%). On repeated distillation the constants were: B.p. 118-119° (2.5 mm),  $n_D^{20}$  1.5240,  $d_4^{20}$  1.4398. The constants for this chloride "in a pure state" are: B.p. 112-113° (1.5 mm),  $n_D^{20}$  1.5233,  $d_4^{20}$  1.4413 [1]. There was no high-boiling fraction.

3. The reaction of phosphorus pentachloride with the isopropenyl ester of n-butyric acid in the presence of acetyl chloride. 9 g of acetyl chloride was added to a suspension of 35.8 g of phosphorus pentachloride in 50 ml of carbon tetrachloride and heated on the water bath to 50°. Then, with stirring, 11 g of isopropenyl butyrate was added drop by drop. This was heated for two hours more at 65-70°, cooled with water, sulfur dioxide passed through; the solvent, thionyl chloride and phosphorus pentachloride distilled off and the remaining material distilled in vacuo. Two low-boiling fractions were collected at the beginning: 1) 70-120° (11 mm) (1.27 g); 2) 120-132° (2.5 mm) (0.9 g),  $n_D^{20}$  1.5150, i.e., not containing the chloride of  $\alpha$ -acetyl- $\beta$ -chloropropenylphosphinic acid ( $n_D^{20}$  1.5240). The third fraction, b.p. 133-135° (2 mm),  $n_D^{20}$  1.5175, was the chloride of  $\alpha$ -butyryl- $\beta$ -chloropropenylphosphinic acid. The yield was 13.8 g (61% compared with 58% in the "pure" experiment [3]). After repeated distillation the yield was 12.8 g (56.6%).

B.p. 132-133° (1.5 mm),  $n_D^{20}$  1.5170,  $d_4^{20}$  1.3398,  $M_R^{20}$  59.51; calc. 56.99.

Found %: C 31.90; H 3.74; P 11.59.  $\text{C}_7\text{H}_{10}\text{O}_2\text{Cl}_3\text{P}$ . Calculated %: C 31.90; H 3.83; P 11.86.

The constants of this chloride as prepared in the "pure" experiment (in the absence of acetyl chloride) were:

B.p. 132-133° (1.5 mm),  $n_D^{20}$  1.5180,  $d_4^{20}$  1.3474 [3].

D. The reaction of phosphorus pentachloride with a mixture of vinyl acetate and isopropyl butyrate. In the cold. A mixture of 8.6 g of vinyl acetate and 12.8 g of the isopropenyl ester of n-butyric acid was added drop by drop, with stirring and cooling to  $-20^{\circ}$ , to a filtered solution of 83.2 g of phosphorus pentachloride in 650 ml of carbon tetrachloride. Stirring was continued for another 1.5 hours. Then the cooling bath was removed and, with continued stirring, the mixture was brought up to room temperature, after which it was heated for one hour at  $40-45^{\circ}$ . During this the entire precipitate went into solution. After cooling with water, sulfur dioxide was passed in; then the solvent, thionyl chloride and phosphorus oxychloride were distilled in vacuo and the remaining material distilled from a flask with a small fractionating column. After triple fractionation, three fractions were obtained, the constants and weights of which are shown in Table 1.

TABLE 1

Fraction	B.p.	$n_D^{20}$	$d_4^{20}$	Quantity in g	Yield (%)	Principal component of the fraction
I	98-99° (2.5 mm)	1.5098	1.5462	18	70	Pure chloride of $\alpha$ -acetyl- $\beta$ , $\beta$ -dichloroethylphosphinic acid
II	113-125 (1 mm)	1.5138	—	3.3	—	Intermediate fraction (mixture of I and IV)
III	125-128 (1 mm)	1.5164	1.3864	3.8	—	Mixture of I and IV; principally IV
IV	128-129 (1 mm)	1.5175	1.3532	4.21	16	Pure chloride of $\alpha$ -butyryl- $\beta$ -chloropropenylphosphinic acid

TABLE 2

Fraction	B.p.	$n_D^{20}$	$d_4^{20}$	Quantity in g	Yield (%)	Principal component of the fraction
I	96-99° (2.5 mm)	1.5120	1.5240	13.1	65	Chloride of $\alpha$ -acetyl- $\beta$ , $\beta$ -dichloroethylphosphinic acid
II	100-103 (2.5 mm)	1.5110	1.5256	3.7	—	Intermediate fraction
III	104-128 (1.5 mm)	1.5150	—	4.4	—	
IV	129-132 (1.5 mm)	1.5165	1.3679	5.4	—	Chiefly contains the chloride of $\alpha$ -butyryl- $\beta$ -chloropropenylphosphinic acid
V	132-133 (1.5 mm)	1.5172	1.3476	8.7	33	Pure chloride of $\alpha$ -butyryl- $\beta$ -chloropropenylphosphinic acid

Analysis of fraction IV showed that it consisted of the chloride of  $\alpha$ -butyryl- $\beta$ -chloropropenylphosphinic acid.

Found %: C 31.36, 31.48; H 3.90, 3.92; P 11.56, 11.96.  $C_7H_{10}O_2Cl_3P$ . Calculated %: C 31.90; H 3.83; P 11.86.

With heating. A mixture of 8.6 g of vinyl acetate and 12.8 g of the isopropenyl ester of n-butyric acid was added drop by drop, with stirring, to a suspension of 83.2 g of phosphorus pentachloride in 100 ml of carbon tetrachloride which had been heated to  $50-55^{\circ}$ . This was stirred for one hour at  $55-60^{\circ}$  and for half an hour at  $60-70^{\circ}$ . After cooling, sulfur dioxide was passed in and then the solvent, thionyl chloride and phosphorus oxychloride were distilled off in vacuo. The remaining material was distilled from a flask equipped with a small fractionating column. The quantities and constants of the fractions obtained after triple fractionation are shown in Table 2.

E. An attempt to rearrange the chloride of  $\beta$ -acetoxy- $\beta$ -chloroethylphosphinic acid in the presence of phosphorus pentachloride. 12.8 g of the chloride of  $\beta$ -acetoxy- $\beta$ -chloroethylphosphinic acid ( $n_D^{20}$  1.4860) was dissolved in 30 ml of dry carbon tetrachloride, then 20.8 g of phosphorus pentachloride was added and the mixture heated on a bath at  $75-80^{\circ}$  for one hour. It was then cooled, sulfur dioxide passed in, the solvent, thionyl chloride and phosphorus oxychloride distilled off and the remaining material distilled in vacuo. 11.6 g (90.6%) of the original hydrocarbon,  $n_D^{20}$ , was recovered.

## SUMMARY

A new intra-molecular rearrangement of the addition products of phosphorus pentachloride and enol esters was found. This occurs by the migration of an acyl group from an oxygen atom to an adjacent carbon atom (joined to phosphorus) and results in the formation of  $\alpha$ -phosphorylated,  $\beta,\beta$ -dichloroketones and  $\beta$ -chlorovinylketones. A scheme for the rearrangement is proposed.

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## DERIVATIVES OF ETHYLENEIMINE

### III. DIETHYLENEIMIDES OF PYRIMIDYLAMIDOPHOSPHORIC ACIDS

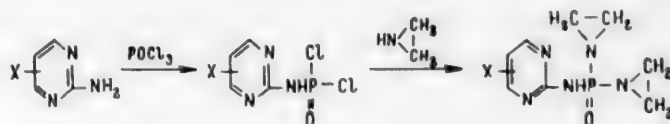
A. A. Kropacheva and N. V. Sagonov

S. Ordzhonikidze Scientific Research Institute  
of Pharmaceutical Chemistry

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The present work is devoted to the preparation of diethyleneimides of pyrimidyl-2-amidophosphoric acids. The preparation of these compounds was carried out starting from 2-aminopyrimidines by a scheme that one of us had described previously [1, 2] for preparing other diethyleneimides of amidophosphoric acids.



The phosphorylation reaction of aminopyrimidines had not been investigated previously by anyone, and no dichlorides of pyrimidylamidophosphoric acids have been reported.

The phosphorylation of the 2-aminopyrimidines was carried out under various conditions, depending on the reactivity of the amino group and the stability of the pyrimidine ring substituents toward acidic reactants.

The preparation of the diethyleneimides of pyrimidyl-2-amidophosphoric acids was accomplished by the interaction of the corresponding acid dichlorides with ethyleneimine in benzene in the presence of triethylamine, with cooling.

In the interaction of 4-chloropyrimidyl-2-amidophosphoric acid dichloride with ethyleneimine, the chlorine in the 4-position of the pyrimidine ring either is retained or is also replaced by ethyleneimine, depending on the reaction conditions.

The pyrimidyl-2-amidophosphoric acid dichlorides are colorless crystalline substances, difficultly soluble in inert organic solvents; they react readily with moist air, with the evolution of hydrogen chloride.

The diethyleneimides of the pyrimidyl-2-amidophosphoric acids are colorless crystalline substances, soluble in the cold in water or alcohol and with heating in benzene, insoluble in ether.

A separate communication will give the biological properties of the compounds obtained.

#### EXPERIMENTAL PART

The 2-aminopyrimidines used in this work are described in the literature. These compounds were prepared by well-known methods [3].

**Pyrimidyl-2-amidophosphoric Acid Dichlorides.** The dichlorides of 4-methoxypyrimidyl-2-, 4-diethylamino-pyrimidyl-2-, and 4,6-dimethylpyrimidyl-2-amidophosphoric acids were prepared by the interaction of the amines with phosphoryl chloride in an inert solvent at 45-50°. A typical experiment is described below. To a solution of 10 ml of freshly distilled phosphoryl chloride in 50 ml of anhydrous benzene, 4 g of 2-amino-4-methoxypyrimidine was added slowly at room temperature, after which the reaction mass was heated to 45-50° and held at this temperature for 5 hr. The precipitate, a mixture of 2-amino-4-methoxypyrimidine hydrochloride and 4-methoxypyrimidyl-2-amidophosphoric acid dichloride, was filtered off, transferred into 150 ml of a 2:1 benzene-chloroform mixture, heated to boiling, and filtered to remove the undissolved 2-amino-4-methoxypyrimidine hydrochloride. The filtrate

evaporated to dryness under vacuum. The residue, 4-methoxypyrimidyl-2-amidophosphoric acid dichloride, was a colorless powder. Yield 2.4 g (62%), m.p. 190° (from benzene).

Found %: Cl 32.69.  $C_4H_4ON_3Cl_2P$ . Calculated %: Cl 33.45.

The 4-diethylaminopyrimidyl-2- and 4,6-dimethylpyrimidyl-2-amidophosphoric acid dichlorides obtained by this method could not be purified successfully for analysis.

The 4-chloropyrimidyl-2- and 5-chloropyrimidyl-2-amidophosphoric acid dichlorides were obtained only by boiling the 2-amino-4-chloro- and 2-amino-5-chloropyrimidines with phosphoryl chloride.

A mixture of 2 g of 2-amino-4-chloropyrimidine and 8 ml of phosphoryl chloride was heated in a 120-130° oil bath until the 2-amino-4-chloropyrimidine was completely dissolved; then the phosphoryl chloride was removed by vacuum distillation, and the residue in the flask was mixed with anhydrous benzene and filtered; the precipitate was washed on the funnel with benzene and ether. Yield 3.7 g (84.3%), m.p. 163-164° (from benzene).

Found %: Cl 43.15.  $C_4H_3ON_3Cl_2P$ . Calculated %: Cl 43.24.

The 5-chloropyrimidyl-2-amidophosphoric acid dichloride obtained similarly melted at 163-163.5° (from benzene).

Found %: Cl 42.44.  $C_4H_3ON_3Cl_2P$ . Calculated Cl 43.24.

The pyrimidyl-2-, 4-methylpyrimidyl-2-, and 4-benzylmethylpyrimidyl-2-amidophosphoric acid dichlorides were prepared by boiling the amine hydrochlorides with phosphoryl chloride.

a) A mixture of 2.8 g of 2-amino-4-methylpyrimidine hydrochloride and 13 ml of phosphoryl chloride was boiled until the hydrochloride was completely dissolved, the excess phosphoryl chloride was removed by vacuum distillation, and the dry residue was washed with ether. Yield 2.46 g (56.5%) of 4-methylpyrimidyl-2-amidophosphoric acid dichloride, which after crystallization from benzene melted at 164-165° (with omission of the capillary, 163°).

Found %: Cl 30.07.  $C_5H_6ON_3Cl_2P$ . Calculated %: Cl 31.38.

b) A mixture of 1.9 g of 2-aminopyrimidine hydrochloride and 10 ml of phosphoryl chloride was heated with phosphoryl chloride refluxing for 6 hr, the reaction mass was cooled, and the precipitate was filtered from the phosphoryl chloride and washed with ether on the funnel. Yield of pyrimidyl-2-amidophosphoric acid dichloride 2.4 g (73.5%), m.p. 171-172° (from benzene).

Found %: Cl 32.69.  $C_4H_4ON_3Cl_2P$ . Calculated %: Cl 33.45.

Similarly, 4-benzylmethylaminopyrimidyl-2-amidophosphoric acid dichloride was obtained with 74% yield, m.p. 190° (from benzene).

Found %: Cl 21.58.  $C_{12}H_{13}ON_4Cl_2P$ . Calculated %: Cl 21.60.

Diethyleneimides of Pyrimidyl-2-amidophosphoric Acids. To a solution of 0.85 g of ethyleneimine and 2.5 g of triethylamine in 60 ml of benzene, 2.4 g of pyrimidyl-2-amidophosphoric acid dichloride was added gradually with stirring and cooling (12°). The reaction mass was stirred 0.5 hr more with cooling, 2 hr at room temperature, and then allowed to stand until the following day. Then the reaction mass heated to boiling and filtered hot to remove the triethylamine hydrochloride. After distilling the benzene from the filtrate, 1.95 g (74%) of the diethyleneimide of pyrimidyl-2-amidophosphoric acid was obtained. Colorless crystals with m.p. 128-129° (from benzene), readily soluble in water or alcohol.

The other diethyleneimides of the pyrimidyl-2-amidophosphoric acids were obtained similarly, except for the diethyleneimide of 4-chloropyrimidyl-2-amidophosphoric acid. In this case the reaction mass, after holding 2 hr at room temperature, was filtered, and the filtrate was evaporated to dryness at 20-25° under vacuum. The residue was recrystallized from alcohol.

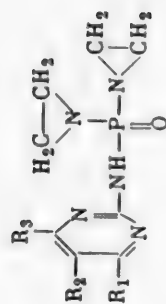
The data on the compounds obtained are presented in the table.

#### SUMMARY

1. Pyrimidyl-2-amidophosphoric acid dichlorides, which have not been reported in the literature, have been prepared.



Diethylenimides of Pyrimidyl-2-amidophosphoric Acid



R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Melting point	Empirical formula	Calculated (%)				Found (%)				Yield (%)
					C	H	N	Cl	C	H	N	Cl	
H	H	H	128—129 •	C <sub>8</sub> H <sub>12</sub> ON <sub>5</sub> P	43.11	5.37	31.10	—	43.11	5.66	31.16	—	78
Cl	H	H	121—12(decomp.) ••	C <sub>8</sub> H <sub>11</sub> ON <sub>5</sub> ClP	—	—	—	13.65	—	—	—	13.48	45
	H	H	129—13(decomp.) ••	C <sub>10</sub> H <sub>13</sub> ON <sub>6</sub> P	45.11	5.69	31.18	—	44.72	5.99	31.35	—	21.6
CH <sub>3</sub> O	H	H	128—129 •	C <sub>9</sub> H <sub>14</sub> O <sub>2</sub> N <sub>5</sub> P	42.35	5.53	27.44	—	42.03	5.46	27.30	—	77
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> N	H	H	151—152.5 •	C <sub>16</sub> H <sub>21</sub> ON <sub>6</sub> P	55.80	6.14	24.4	—	55.78	6.40	—	—	48
CH <sub>3</sub>	H	H	123—124 •	C <sub>9</sub> H <sub>14</sub> ON <sub>6</sub> P	45.18	5.89	29.28	—	45.09	5.95	29.36	—	75.8
H	Cl	H	157—15(decomp.) •	C <sub>8</sub> H <sub>11</sub> ON <sub>5</sub> ClP	37.03	4.28	27.39	13.65	37.24	4.19	27.03	13.66	83.4
(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> N	H	H	150—150.5 •	C <sub>12</sub> H <sub>21</sub> ON <sub>6</sub> P	48.64	7.14	28.37	—	48.85	7.03	28.69	—	53.8
CH <sub>3</sub>	H	CH <sub>3</sub>	128—129 •	C <sub>10</sub> H <sub>16</sub> ON <sub>5</sub> P	47.42	6.37	27.65	—	48.03	6.58	28.14	—	80.8

• From benzene.

•• From alcohol.

2. Diethyleneimides of pyrimidyl-2-amidophosphoric acids, which have not been reported in the literature, have been prepared.

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# ORGANIC INSECTOFUNGICIDES

## LX. INTERACTION OF ESTERS OF THIO- AND DITHIOPHOSPHORIC ACIDS WITH SECONDARY AMINES

N. N. Mel'nikov, B. A. Khaskin, and K. D. Shvetsova -  
Shilovskaya

Scientific Institute of Fertilizers and Insectofungicides  
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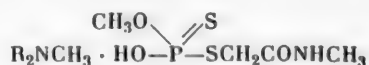
It was demonstrated recently in our laboratory that the interaction of esters of thio- and dithiophosphoric acids with tertiary amines results in the formation of salts of quaternary ammonium bases [1], and the esters of the phosphoric acids show their value as alkylating and arylating agents. Almost simultaneously with our work, analogous sulfonium and ammonium salts were synthesized by German investigators, who studied the interaction of certain tertiary amines and dimethyl sulfide with the simplest esters of thiophosphoric acid having insecticidal activity [2, 3]. In all of the cases studied up to the present, the reaction of tertiary amines with esters of phosphoric acids proceeds simply, with the formation of salts of quaternary ammonium bases, which cannot explain the differing insecticidal activity of esters of phosphoric, thiophosphoric, and dithiophosphoric acids.

In the progress of our earlier studies there was undertaken a study of the reaction of esters of phosphoric acids with primary and secondary amines. As a result of this investigation, it was established successfully that the reaction of different esters of phosphoric acids with secondary amines proceeds differently, depending of the structure of the initial ester.

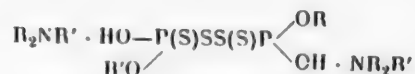
The interaction of aliphatic and aliphatic-aromatic esters of thiophosphoric acid with secondary amines occurs with the formation of salts of a tertiary amine.



An analogous reaction occurs with certain esters of dithiophosphoric acid. Thus, for example, O,O-dimethyl-S-(N-methylamidomethyl) dithiophosphate (Phosphamide) also forms the corresponding addition product



Salts of tertiary amines are also obtained on the interaction of secondary amines with dialkylthiophosphone disulfides



In contrast to the aliphatic and aliphatic-aromatic esters, aromatic esters of thiophosphoric acid on interaction with secondary amines form amides of diarylthiophosphoric acids.



The structure of the amides obtained in this reaction was proven both by infrared spectra and by counter-synthesis from the amine and diaryl chlorothiophosphate.

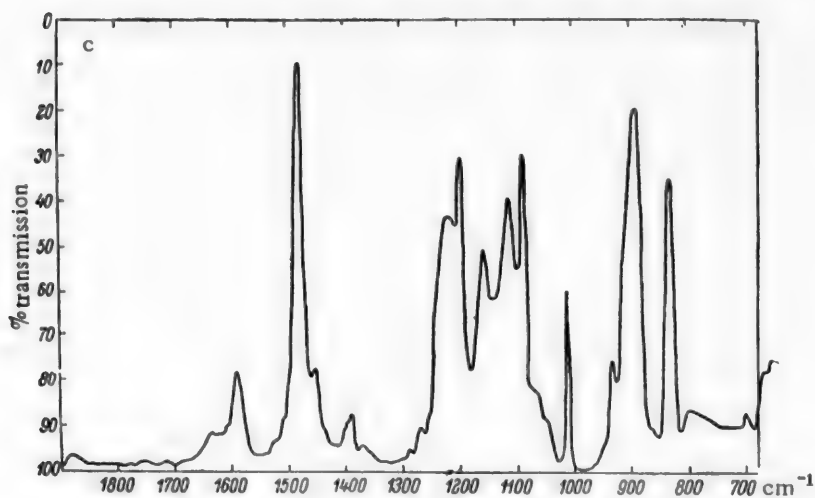
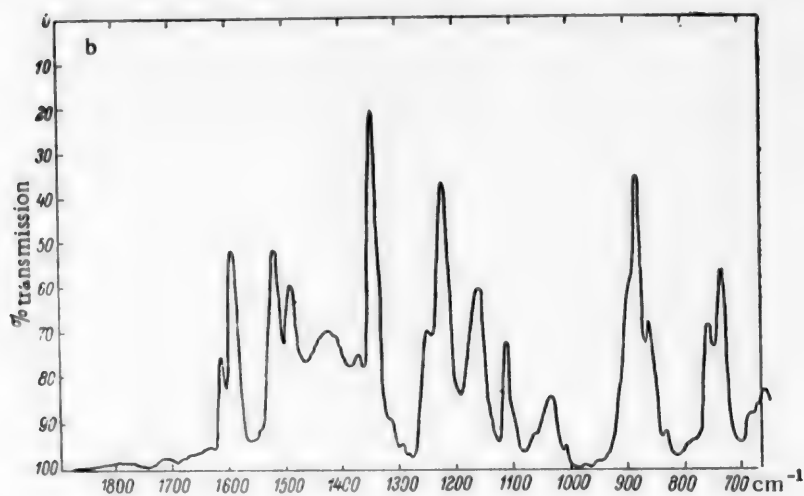
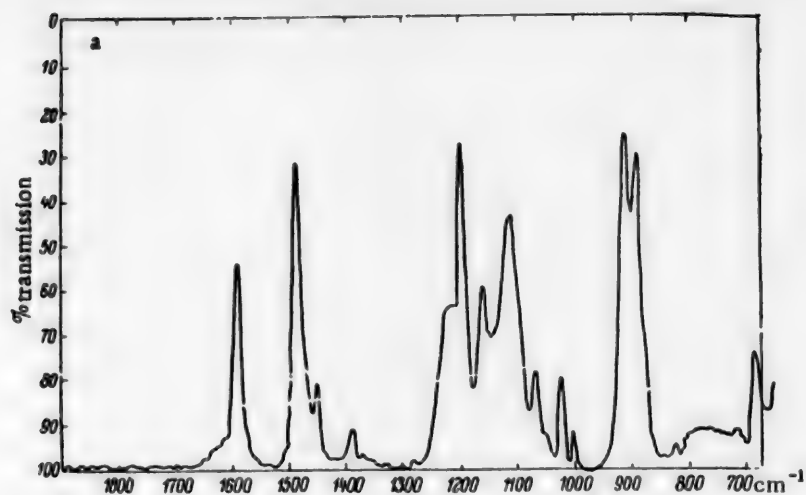
## Properties of Reaction Products from Secondary Amines and Esters of Phosphoric Acids

No	Starting compound	Secondary amine	Compound obtained
1	$(\text{C}_6\text{H}_5\text{O})_2\text{P}=\text{S}$	$(\text{C}_2\text{H}_5)_2\text{NH}$	$(\text{C}_6\text{H}_5\text{O})_2\text{P}=\text{S}\cdot\text{N}(\text{C}_2\text{H}_5)_2$
2	$(\text{O}_2\text{N}-\text{C}_6\text{H}_4\text{O})_2\text{P}=\text{S}$	" "	$(\text{O}_2\text{N}-\text{C}_6\text{H}_4\text{O})_2\text{P}=\text{S}\cdot\text{N}(\text{C}_2\text{H}_5)_2$
3	$(\text{Cl}-\text{C}_6\text{H}_4\text{O})_2\text{P}=\text{S}$	" "	$(\text{Cl}-\text{C}_6\text{H}_4\text{O})_2\text{P}=\text{S}\cdot\text{N}(\text{C}_2\text{H}_5)_2$
4	$(\text{O}_2\text{N}-\text{C}_6\text{H}_4\text{O})_2\text{P}=\text{S}$	$\text{C}_6\text{H}_{11}\text{NH}$	$(\text{O}_2\text{N}-\text{C}_6\text{H}_4\text{O})_2\text{P}=\text{S}\cdot\text{N}(\text{C}_6\text{H}_{11})$
5	$\text{C}_6\text{H}_5\text{O}-\text{P}(\text{S})(\text{CH}_3)_2$	$(\text{C}_2\text{H}_5)_2\text{NH}$	$\text{C}_6\text{H}_5\text{O}-\text{P}(\text{S})(\text{CH}_3)_2\cdot\text{N}(\text{C}_2\text{H}_5)_2$
6	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{O}-\text{C}_6\text{H}_4\text{NO}_2$	" "	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{O}-\text{C}_6\text{H}_4\text{NO}_2\cdot\text{N}(\text{C}_2\text{H}_5)_2$
7	$(\text{C}_6\text{H}_5\text{O})_2\text{P}(\text{S})-\text{O}-\text{C}_6\text{H}_4\text{NO}_2$	" "	$(\text{C}_6\text{H}_5\text{O})_2\text{P}(\text{S})-\text{O}-\text{C}_6\text{H}_4\text{NO}_2\cdot\text{N}(\text{C}_2\text{H}_5)_2$
8	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{O}-\text{C}_6\text{H}_2\text{Cl}_2$	" "	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{O}-\text{C}_6\text{H}_2\text{Cl}_2\cdot\text{N}(\text{C}_2\text{H}_5)_2$
9	$(\text{CH}_3\text{O})_2\text{P}=\text{S}$	" "	$(\text{CH}_3\text{O})_2\text{P}=\text{S}\cdot\text{N}(\text{C}_2\text{H}_5)_2$
10	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{OCH}_2\text{CH}_2\text{SC}_6\text{H}_5$	" "	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{OCH}_2\text{CH}_2\text{SC}_6\text{H}_5\cdot\text{N}(\text{C}_2\text{H}_5)_2$
11	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{SCH}_2\text{C}(=\text{O})\text{NHCH}_3$	" "	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{SCH}_2\text{C}(=\text{O})\text{NHCH}_3\cdot\text{N}(\text{C}_2\text{H}_5)_2$
12	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{S}-\text{S}-\text{P}(\text{OCH}_3)_2$	" "	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{S}-\text{S}-\text{P}(\text{OCH}_3)_2\cdot\text{N}(\text{C}_2\text{H}_5)_2$
13	$(\text{C}_6\text{H}_5\text{O})_2\text{P}(\text{S})-\text{S}-\text{S}-\text{P}(\text{OC}_6\text{H}_5)_2$	" "	$(\text{C}_6\text{H}_5\text{O})_2\text{P}(\text{S})-\text{S}-\text{S}-\text{P}(\text{OC}_6\text{H}_5)_2\cdot\text{N}(\text{C}_2\text{H}_5)_2$
14	$(\text{iso}-\text{C}_6\text{H}_7\text{O})_2\text{P}(\text{S})-\text{S}-\text{S}-\text{P}(\text{OC}_6\text{H}_7\text{-iso})_2$	" "	$(\text{iso}-\text{C}_6\text{H}_7\text{O})_2\text{P}(\text{S})-\text{S}-\text{S}-\text{P}(\text{OC}_6\text{H}_7\text{-iso})_2\cdot\text{N}(\text{C}_2\text{H}_5)_2$
15	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{O}-\text{C}_6\text{H}_2\text{Cl}_2$	$\text{C}_6\text{H}_{11}\text{NH}$	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{O}-\text{C}_6\text{H}_2\text{Cl}_2\cdot\text{N}(\text{C}_6\text{H}_{11})$
16	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{SCH}_2\text{C}(=\text{O})\text{NHCH}_3$	" "	$(\text{CH}_3\text{O})_2\text{P}(\text{S})-\text{SCH}_2\text{C}(=\text{O})\text{NHCH}_3\cdot\text{N}(\text{C}_6\text{H}_{11})$
17	$(\text{C}_6\text{H}_5\text{O})_2\text{P}(\text{S})-\text{S}-\text{S}-\text{P}(\text{OC}_6\text{H}_5)_2$	" "	$(\text{C}_6\text{H}_5\text{O})_2\text{P}(\text{S})-\text{S}-\text{S}-\text{P}(\text{OC}_6\text{H}_5)_2\cdot\text{N}(\text{C}_6\text{H}_{11})$

\* Found %: Cl 26.05. Calculated %: Cl 26.15.

Properties of Reaction Products from Secondary Amines and Esters of Phosphoric Acids  
(continued)

Melting point	$n_D^{20}$	Yield (%)	Found %			Empirical formula	Calculated %		
			N	S	P		N	S	P
114—114.5°	—	43	3.89	9.94	—	$C_{16}H_{20}O_2NSP$	4.36	9.97	—
173—173.5	—	80	10.09	—	7.36	$C_{16}H_{18}O_6N_3SP$	10.22	—	7.53
151—152	—	32	3.39	—	8.02	$C_{16}H_{18}O_2Cl_2NSP$	3.61	—	7.98
158.5—159	—	67	9.89	—	7.19	$C_{17}H_{18}O_6N_3SP$	9.93	—	7.32
—	1.5472	80	7.99	—	8.63	$C_{13}H_{23}O_5N_2SP$	7.99	—	8.84
91—92	—	60	8.46	—	9.19	$C_{12}H_{21}O_5N_2SP$	8.33	—	9.21
—	1.5420	28	7.70	—	8.46	$C_{14}H_{25}O_5N_2SP$	7.69	—	8.50
102—103	—	69	3.66	—	7.77	$C_{12}H_{19}O_3Cl_3NSP$	3.55	—	7.85
—	1.4915	87	5.57	14.23	—	$C_7H_{20}O_3NSP$	6.11	13.99	—
—	1.5019	73	4.43	21.28	—	$C_{10}H_{26}O_3NS_2P$	4.62	21.14	—
—	1.5387	60	9.07	—	10.30	$C_9H_{23}O_3N_2S_2P$	9.26	—	10.24
81—82	—	78	5.84	27.88	—	$C_{12}H_{34}O_4N_2S_4P_2$	6.08	27.85	—
84.5—85	—	63	5.38	24.69	—	$C_{16}H_{42}O_4N_2S_4P_2$	5.42	24.82	—
82.5—84	—	51	5.01	—	10.52	$C_{20}H_{50}O_4N_2S_4P_2$	4.89	—	10.82
98—98.5	—	89	3.79	—	—	$C_{13}H_{19}O_3Cl_3NSP \cdot$	3.44	—	—
—	1.5570	92	8.97	—	10.04	$C_{10}H_{23}O_3N_2S_2P$	8.91	—	9.85
—	1.5449	59	5.51	—	11.25	$C_{18}H_{42}O_4N_2S_4P_2$	5.18	—	11.46



IR spectra of amides of diarylthiophosphoric acid  $R_2P \begin{smallmatrix} S \\ \diagup \diagdown \\ N(C_2H_5)_2 \end{smallmatrix}$

a)  $R =$    $-O-$ ; solvent  $CHCl_3$ ; concentration 0.1586 mole/liter;

b)  $R = O_2N-$    $-O-$ ; solvent  $CH_3CN$ ; concentration 0.07573 mole/liter;

c)  $R = Cl-$    $-O-$ ; solvent  $CHCl_3$ ; concentration 0.1894 mole/liter.



The compounds obtained and their properties are shown in the table. The IR spectra of the compounds are given in the figure (a, b, c).\*

## EXPERIMENTAL PART

1. Interaction of Amines with Aliphatic and Aliphatic-Aromatic Esters of Thiophosphoric Acid. We cite as an example the description of the preparation of the methyldiethylamine salt of O-methyl-O-2,4,5-trichlorophenylthiophosphoric acid.

To a solution of 0.01 mole of O,O-dimethyl-O-2,4,5-trichlorophenyl thiophosphate in 30 ml of absolute ether, there was added 0.02 mole of diethylamine, and the resulting mixture was held several days at 20-25°. After completion of the reaction, the solvent was distilled off, and the residue was extracted with boiling petroleum ether. After cooling the petroleum ether solution, a white crystalline substance was precipitated, with m.p. 102-103° (see table, no. 8).

Reaction of the amines with the other esters of thiophosphoric acid was conducted under analogous conditions. The compounds obtained and their properties are shown in the table.

2. Interaction of Amines with bis(Dialkoxothiophosphone) Disulfides. As an example of this reaction, we cite the interaction of bis(diethoxythiophosphone) disulfide with diethylamine.

To a solution of 0.005 mole of bis(diethoxythiophosphone) disulfide in absolute ether, 0.02 mole of diethylamine was added. A white crystalline precipitate of the salt had already started to form in 10-15 min. The crystals were filtered off and washed 3-4 times with absolute ether. After washing, the preparation was obtained in analytically pure form (see table, no. 13).

The reaction of diethylamine with other bis(dialkoxothiophosphone) disulfides were carried out under identical conditions. The compounds obtained and their properties are shown in the table.

3. Interaction of Amines with Triaryl Thiophosphates. The reaction of triaryl thiophosphates with secondary amines was conducted under the following conditions: To a solution of 0.01 mole of triphenyl thiophosphate in 25 ml of absolute ether, there was added 0.02 mole of diethylamine, and the resulting mixture was held for several days at 20-25°. To recover the reaction product, the reaction mixture was diluted with petroleum ether and refluxed 10-15 min on a steam bath. The crystals that precipitated on cooling were filtered off and dissolved in a small quantity of anhydrous ethanol. The amide was precipitated from the alcohol solution with petroleum ether at -20°. The resulting product did not give any melting point depression in a mixed sample with the diethylamide of diphenylthiophosphoric acid synthesized from diphenyl chlorothiophosphate and diethylamine. The infrared spectra of these two substances were also identical (see table, no. 1).

Amides were synthesized from tri-nitrophenyl thiophosphate and tri-4-chlorophenyl thiophosphate under analogous conditions. The properties of the compounds synthesized are shown in the table.

## SUMMARY

A study had been made of the interaction of secondary amines with esters of thiophosphoric and dithiophosphoric acids, and also with bis(dialkoxothiophosphone) disulfides. It has been demonstrated that the reaction with secondary amines occurs differently, depending on the structure of the ester. Aliphatic and aliphatic-aromatic esters prove their value as alkylating agents, but aromatic esters enter into an exchange reaction, forming amides of a diarylthiophosphoric acid.

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\*The IR spectra were taken by A. F. Vasil'ev, for which the authors take the opportunity to express deep gratitude to him.

## DERIVATIVES OF 3-AMINOPHENOL

### II. O-BENZENESULFONYL AND O,N-DI(BENZENESULFONYL)

#### DERIVATIVES OF 3-AMINOPHENOL AND ITS HOMOLOGS

I. V. Aleksandrov and Yu. S. Abradushkin

Scientific Research Institute of Organic Intermediates and Dyes

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In a continuation of work in a search for the components of color development [1], we synthesized O-benzene-sulfonyl and O,N-di(benzenesulfonyl) derivatives of 3-aminophenol (I), 2-amino-4-hydroxytoluene (II), 4-amino-2-hydroxytoluene (III), 3-amino-5-hydroxytoluene (IV), 3-amino-5-hydroxy-1,2-xylene (V), 5-amino-3-hydroxy-1,2-xylene (VI), and 2-amino-6-hydroxy-1,4-xylene (VII).

The O-benzenesulfonyl derivatives of (I-VII) were synthesized by acylation of the nitrophenols with benzene sulfochloride [benzenesulfonyl chloride] in aqueous sodium carbonate medium [2] and reduction of the resulting nitroacylphenols with hydrazine hydrate on skeletal nickel catalyst [3]. By acylation of the amino group of the resulting O-acylated derivatives with benzene sulfochloride in aqueous medium in the presence of sodium acetate [4], the O,N-diacyl derivatives of (I-VII) were obtained.

Some of the physicochemical properties of the synthesized compounds were studied. It was established that the O-mono and O,N-di(benzenesulfonyl) derivatives of (I-VII), the same as the O-benzenesulfonyl derivatives of 3-nitrophenol and its homologs, do not fluoresce in ultraviolet light.

#### EXPERIMENTAL PART

2-Nitro-4-hydroxytoluene, 3-nitro-5-hydroxytoluene, 4-nitro-2-hydroxytoluene, 3-nitro-5-hydroxy-1,2-xylene, 5-nitro-3-hydroxy-1,2-xylene, and 2-nitro-6-hydroxy-1,4-xylene were synthesized by methods described previously [1].

O-Benzenesulfonyl Derivatives of 3-Nitrophenol and Its Homologs. A mixture of 0.01 mole of 3-nitrophenol or its homolog, 0.011 mole of benzene sulfochloride, and 0.011 mole of calcined sodium carbonate in 30 ml of water was stirred 3 hr at 95-100°. After cooling to 20°, the precipitate was filtered off, washed with 10 ml of water, and recrystallized from methanol or aqueous methanol with the addition of activated carbon (Table 1).

O-Benzenesulfonyl Derivatives of 3-Aminophenol and Its Homologs. A 0.01 mole quantity of the nitro compound was dissolved in methanol (concentration 0.1 g/ml), 0.03 mole of hydrazine hydrate was added, the solution was heated to boiling, 0.1-0.2 g of a paste of skeletal nickel was added (about 50%), and the mixture was boiled until the solution was decolorized. For decomposition of the excess hydrazine hydrate, 0.1 g of a paste of skeletal nickel was added, then the metallic nickel was filtered off and about 75% of the methanol was distilled off. The material that precipitated on cooling was filtered off, washed with 1-2 ml methanol, dried, and recrystallized from aqueous methanol with the addition of activated carbon.

In the preparation of the 3-benzenesulfoxyaniline, the order of introducing the ingredients was changed, thus: To a methanol solution of the nitro compound, the skeletal nickel paste was added; then the hydrazine hydrate was added slowly while boiling. The remainder of the process was carried out as indicated above (Table 2).

O,N-Di(benzenesulfonyl) Derivatives of 3-Aminophenol and Its Homologs. A mixture of 0.01 mole of the O-acyl derivative of 3-aminophenol or its homolog, 0.011 mole of benzene sulfochloride, and 0.011 mole of sodium acetate in 30 ml water was stirred 6 hr at 100°. After cooling to 20°, the precipitate was filtered off, washed with 10 ml of water, and recrystallized from aqueous methanol with the addition of activated carbon (Table 3).

TABLE 1. O-Benzzenesulfonyl Derivatives of 3-Nitrophenol and Its Homologs

No.	Compound	Yield (%)	M.p.	Color and crystalline form	Solvent (ml/g)	Found (%)		Empirical formula	Calc. (%)	
						N	S		N	S
1	1-Nitro-3-benzenesulfoxybenzene	72.6	71-72° 72-73 [5]	Yellow plates	10 ml 90% methanol	5.00, 4.88		C <sub>11</sub> H <sub>9</sub> O <sub>2</sub> NS	5.02	
2	2-Nitro-4-benzenesulfoxytoluene	76.8	80-81	Yellow prisms	10 ml methanol	5.03, 5.04	10.69, 10.70	C <sub>11</sub> H <sub>11</sub> O <sub>2</sub> NS	4.78	10.93
3	4-Nitro-2-benzenesulfoxytoluene	85.5	98	Colorless prisms	15 ml methanol	5.02, 5.07	10.74, 10.71	C <sub>11</sub> H <sub>11</sub> O <sub>2</sub> NS	4.78	10.93
4	3-Nitro-5-benzenesulfoxytoluene	80.6	101-102	Yellow needles	15 ml methanol	4.60, 4.77		C <sub>11</sub> H <sub>11</sub> O <sub>2</sub> NS	4.78	
5	3-Nitro-5-benzenesulfoxy-1,2-xylene	75.4	79-80	Yellow needles	15 ml methanol	4.68, 4.72		C <sub>11</sub> H <sub>11</sub> O <sub>2</sub> NS	4.56	
6	5-Nitro-3-benzenesulfoxy-1,2-xylene	82.6	106.5-107	Yellow plates	10 ml methanol	4.44, 4.13		C <sub>11</sub> H <sub>11</sub> O <sub>2</sub> NS	4.56	
7	2-Nitro-6-benzenesulfoxy-1,4-xylene	81.5	79.5	Colorless prisms	40 ml 75% methanol	4.15, 4.21		C <sub>11</sub> H <sub>11</sub> O <sub>2</sub> NS	4.56	

TABLE 2. O-Benzenesulfonyl Derivatives of 3-Aminophenol and Its Homologs

No.	Compound	Yield (%)	M.p.	Color and crystalline form	Solvent (ml/g)	Found %				Empirical formula	Calculated %			
						C	H	N	S		C	H	N	S
1	1-Amino-3-benzenesulfonylbenzene	92.1	51—52°	Colorless needles	40 ml 20% methanol	—	—	5.48, 5.63	—	$C_{12}H_{11}O_3NS$	—	—	5.62	—
2	2-Amino-4-benzenesulfonyltoluene	94.5	78—79	Colorless needles	15 ml 75% methanol	—	—	5.44, 5.59	12.12, 12.14	$C_{13}H_{13}O_3NS$	—	—	5.32	12.18
3	4-Amino-2-benzenesulfonyltoluene	84.3	101—102	Colorless plates	70 ml 50% methanol	59.09, 59.04	5.18, 5.30	—	12.26, 12.27	$C_{13}H_{13}O_3NS$	59.30	4.98	—	12.18
4	5-Amino-3-benzenesulfonyltoluene	71.3	118—119	Colorless prisms	30 ml 20% methanol	—	—	5.37, 5.55	—	$C_{13}H_{13}O_3NS$	—	—	5.32	—
5	3-Amino-5-benzenesulfonyl-1,2-xylene	93.2	94—95	Colorless plates	30 ml 60% methanol	—	—	4.82, 4.72	—	$C_{14}H_{15}O_3NS$	—	—	5.05	—
6	5-Amino-3-benzenesulfonyl-1,2-xylene	79.1	91—92	Colorless prisms	40 ml 60% methanol	—	—	4.94, 5.12	—	$C_{14}H_{15}O_3NS$	—	—	5.05	—
7	2-Amino-6-benzenesulfonyl-1,4-xylene	82.0	114—115	Colorless plates	30 ml 60% methanol	—	—	4.68, 4.66	—	$C_{14}H_{15}O_3NS$	—	—	5.05	—

TABLE 3. O,N-Di(benzenesulfonyl) Derivatives of 3-Aminophenol and Its Homologs

No.	Compound	Yield (%)	M.p.	Color and crystalline Form	Solvent (ml/g)	Found (%)		Empirical formula	Calculated (%)	
						N	S		N	S
1	1-Benzenesulfamino-3-benzenesulfoxy-benzene	79.6	111—112°	Colorless prisms	40 ml 60% methanol	3.55, 3.55		$C_{18}H_{15}O_3NS_2$	3.60	
2	2-Benzenesulfamino-4-benzenesulfoxy-toluene	70.0	128.5—129.5	Colorless prisms	30 ml 80% methanol	3.67, 3.56	15.94, 15.96	$C_{19}H_{17}O_3NS_2$	3.47	15.89
3	4-Benzenesulfamino-2-benzenesulfoxy-toluene	73.3	117.5—118.5	Colorless prisms	40 ml 60% methanol	3.32, 3.24	15.86, 16.03	$C_{19}H_{17}O_3NS_2$	3.47	15.89
4	3-Benzenesulfamino-5-benzenesulfoxy-toluene	60.3	103	Colorless prisms	30 ml 75% methanol	3.42, 3.29		$C_{19}H_{17}O_3NS_2$	3.47	
5	3-Benzenesulfamino-5-benzenesulfoxy-1,2-xylene	72.3	94—95	Colorless plates	30 ml 60% methanol	3.27, 3.26		$C_{20}H_{19}O_3NS_2$	3.36	
6	5-Benzenesulfamino-3-benzenesulfoxy-1,2-xylene	71.1	128—129	Colorless plates	15 ml 75% methanol	3.08, 3.28		$C_{20}H_{19}O_3NS_2$	3.36	
7	2-Benzenesulfamino-6-benzenesulfoxy-1,4-xylene	51.3	148—149	Colorless prisms	80 ml 60% methanol	3.31, 3.51		$C_{20}H_{19}O_3NS_2$	3.36	

## SUMMARY

O-Benzenesulfonyl and O,N-di(benzenesulfonyl) derivatives of 3-aminophenol and its homologs have been synthesized. Some of the properties of the synthesized compounds have been studied.

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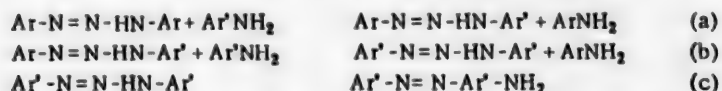
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The reaction of rearrangement of symmetrical triazenes to orthoaminoazo dyes differing in molecular structure from the initial triazene components is connected with complex conversions and can occur only if a triazene rearrangement occurs initially: The original symmetrical triazene on splitting interacts with one mole of the amine of the medium and is converted first to an intermediate unsymmetrical triazene, which then is converted with a second mole of the amine of the medium to a symmetrical triazene in which the structure of both components corresponds to that of the amine of the medium. The new symmetrical triazene that is formed is subjected to the aminoazo rearrangement in the corresponding orthoaminoazo compound.

The triazene conversion reaction may be represented in general form by the following scheme:



In the end, as a result of the two-step triazene rearrangement (Eqs. a and b) and the subsequent aminoazo rearrangement (Eq. c), both aromatic components of the original triazene are replaced completely by the amine of the medium.

However, the reaction follows the course indicated above only if the aromatic amine of the medium has a greater number of alkyl substituents than does the aromatic amine entering into the structure of the original triazene. If the aromatic amine of the medium is less alkylated than the components of the original symmetrical triazene, then there is observed rearrangement of the triazene to the corresponding symmetrical orthoaminoazo dye. From the triazene (VI) in p-toluidine or aniline medium, the orthoaminoazo compound (IV) is formed, and from 1,3-bis(3', 4', 5'-trimethylphenyl)-triazene (X), the orthoaminoazo compound (IX) is formed. The symmetrical triazene (VI) in the presence of an aromatic amine without an alkyl substituent (aniline) also forms the orthoaminoazo (IV) (Table).

In certain cases in the presence of an amine with an unsubstituted para-position (e.g., aniline) the rearrangement of the triazene (VI) has a somewhat more complex character, a strong tendency toward para-substitution beginning to be manifested; in addition to the orthoaminoazo compound (IV), small quantities of paraaminoazo compound are obtained: 4-aminoazobenzene (VII), which is a substance formed completely from the amine of the medium, and the unsymmetrical 3,4-dimethyl-4'-aminoazobenzene (VIII), which is a substance formed from one molecule of the more highly ring-alkylated component of the triazene (VI) and one molecule of the amine of the medium (aniline). Apparently in this case there is a rearrangement of the unsymmetrical triazene to the unsymmetrical para-aminoazo compound (VIII) according to the equation



and a rearrangement of the newly formed symmetrical triazene (which corresponds fully to the amine of the medium) to the symmetrical 4-aminoazobenzene (VII) according to Eq. (c).

The formation of the unsymmetrical 4-methyl-4'-aminoazobenzene (III) from 1,3-bis(4'-tolyl)-triazene (V) in the presence of aniline was observed previously [4].

By the same route, as a result of rearrangement of the unsymmetrical 1-(3', 4'-dimethylphenyl)-3-phenyltriazene (XII) in the presence of p-toluidine, 3,4-dimethyl-6-(4'-tolylazo)-aminobenzene (XIII) is obtained (table).

It should be noted that under the conditions of the usual azo coupling of phenyldiazonium chloride with the hydrochloride of aniline or 3,4-dimethylaminobenzene, no azo dye is formed. Only with very prolonged coupling (more than 48 hours) at 0° was there obtained a small quantity (about 1%) of 4-aminoazobenzene [5]; however, it is not excluded that this reaction also takes place only as a result of rearrangement of the diazoamino compound that is first formed.

The rearrangement of symmetrical triazenes goes in the direction of increasing the basicity of the aromatic amine, depending on the positive inductive effect of the methyl groups, i.e., in the direction of creating a greater electron density in the ortho position to the orienting amino group (in proportion to the increase of alkyl substituents in the ring), which is in agreement with the results we obtained for the rearrangement of unsymmetrical triazenes [1].

Up to recently, views on the mechanisms of the diazoamino-aminoazo rearrangement have reduced to a consideration of this rearrangement as an electrophilic intermolecular reaction occurring under the action of an acid which catalyzes this process through the stage of splitting of the triazene and the formation of the aryldiazonium chloride and the free amine which then enter into the usual azo coupling [4-9]. However, the results of our investi-

Triazene	Medium	Azo compound obtained	M.p.	Found (%)			Calc. (%)		
				C	H	N	C	H	N
1,3-Diphenyltriazene (I) - light yellow leaflets, m.p. 98-99°	p-Toluidine	4-Methyl-6-(4'-tolylazo)-aminobenzene (II) - yellow plates	115-116°	74.63, 74.31	6.94 6.72	18.62, 18.88	74.63	6.70	18.65
	3,4-Dimethylaminobenzene	3,4-Dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV) - orange plates	185-186°	63.5					
1,3-Bis(4'-tolyl)-triazene (V) - yellowish needles, m.p. 116-117°	Aniline [4]	4-Methyl-4'-aminoazobenzene (III)	184-185°	53.5					
	3,4-Dimethylaminobenzene	3,4-Dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV) - orange plates	185-186	37.5	75.86, 76.00	16.74, 16.69	75.85	7.56	16.58
	Aniline	1) 3,4-Dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV) - orange plates 2) 4-Aminoazobenzene (VII) - yellow prisms	124-125°						
1,3-Bis(3',4'-dimethylphenyl)-triazene (VI) - yellow prisms, m.p. 141-142° (decomp.)	p-Toluidine	3) 3,4-Dimethyl-4'-aminoazobenzene (VIII) - dark orange prisms 3,4-Dimethyl-4'-dimethylphenylazo)-aminobenzene (IV) - orange plates	128-129° 169-170	50.0	75.53 75.60	16.31, 16.42	75.85	7.56	16.58
	3,4,5-Trimethylaminobenzene	3,4,5-Trimethyl-6-(3',4',5'-trimethylphenylazo)-aminobenzene (IX) - orange plates	160-162		76.93, 77.05	15.13, 14.91	76.82	8.23	14.93
1,3-Bis(3',4',5'-trimethylphenyl)-triazene (X) - dark yellow needles, m.p. 140.5-142° (decomp.)	3,4-Dimethylaminobenzene	3,4,5-Trimethyl-6-(3',4',5'-trimethylphenylazo)-aminobenzene (IX) - orange plates	150-151	40.0	76.67, 76.51	14.80, 14.77	76.82	8.23	14.93
1-(3',4'-Dimethylphenyl)-3-(4'-tolyl)-triazene (XI) - yellowish plates, m.p. 111-112° (decomp.)	Aniline	3,4-Dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IX) - orange plates	184-185	18.0	75.50, 75.45	16.43, 16.60	75.85	7.56	16.58
1-(3',4'-Dimethylphenyl)-3-phenyltriazene (XII) - yellowish plates, m.p. 95.5-96° (decomp.)	p-Toluidine	3,4-Dimethyl-6-(4'-tolylazo)-aminobenzene (XIII) - orange prisms	157-159°	43.5					

\* Does not give any melting point depression with known (IV) obtained according to data of [13].

\*\* Does not give any melting point depression with known (VII).

\*\*\* Does not give any melting point depression with known material obtained according to data of [1].

gations, both on the rearrangement of unsymmetrical triazenes [1] and on the rearrangement of symmetrical triazenes in the presence of an aromatic amine differing in structure from the original triazene components provide a basis for proposing another mechanism for the rearrangement.

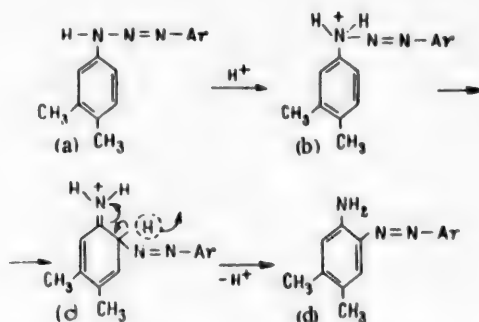
The conversion reaction of aromatic triazenes in the presence of hydrochloric acid or amine hydrochlorides has a complex character and consists of a number of concurrent reactions.

1. Splitting of the triazene into an aryldiazonium chloride and an amine. In concentrated hydrochloric acid, 1,3-diphenyltriazene forms quantitatively phenyldiazonium chloride and aniline [5].
2. Azo coupling of the aryldiazonium chloride (that is formed from the triazene under the influence of hydrochloric acid) with a new active azo component (typical reaction of electrophilic substitution). Thus, from 1,3-diphenyltriazene after treatment with concentrated hydrochloric acid and subsequent azo coupling with phenol, 4-hydroxyazobenzene is obtained [10, 11], and with  $\beta$ -naphthol,  $\alpha$ -phenylazo- $\beta$ -naphthol [5]. These compounds are also obtained readily by direct azo coupling.
3. Triazene rearrangement—recombination of the aryldiazonium chloride (formed from the triazene) with a new and as a rule more active aromatic amine into a new triazene (electrophilic intermolecular reaction). This rearrangement was discovered by Goldschmidt [12] in the example of rearrangement of 1,3-diphenyltriazene, 1-(4'-tolyl)-3-phenyltriazene, and 1,3-bis(2',4',5'-trimethylphenyl)-triazene to 1,3-bis(4'-tolyl)-triazene in the presence of *p*-toluidine and its hydrochloride, and also the rearrangement of 1,3-bis(4'-tolyl)-triazene to 1-(4'-tolyl)-3-phenyltriazene in the presence of aniline and its hydrochloride. The reactions investigated in our work also can proceed only through independent triazene rearrangements.
4. Aminoazo rearrangement of the original or newly formed triazene to an aminoazo compound—an intramolecular reaction. As it follows from the results of our previous investigation, this reaction cannot go through azo coupling of a diazonium chloride and an aromatic amine [1]. It should be noted that up to the present time it has been impossible to give a satisfactory explanation for the fact that the usual azo coupling, which does not occur with certain amines in acidic medium, occurs with those same substances formed on splitting of a diazoamino compound.

The aminoazo rearrangement has a slower rate than the triazene rearrangement; if the reverse were true, in the rearrangement of 1,3-diphenyltriazene in 3,4-dimethylaminobenzene medium, 4-aminoazobenzene would be obtained, and not the 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV) that is actually formed.

We have shown that the rearrangement of the triazene (VI) to the azo dye (IV) in a medium of chlorobenzene and hydrochloric acid, but without any aromatic amine, proceeds with a 42% yield. This yield is only slightly below the yield of azo dye obtained as a result of rearrangement in that same medium in an excess of aromatic amine (50% [yield]). These data are evidence in favor of the intramolecular character of the aminoazo rearrangement.

The mechanism of the intramolecular orthoaminoazo rearrangement can be represented by the following scheme.



Initially, as a result of addition of a proton to the triazene molecule (a), the cation (b) is formed; then, as a result of isomerization, possibly going through the intermediate structure (c), and subsequent removal of the proton, the orthoaminoazo compound (d) is formed.

## EXPERIMENTAL PART

**Preparation of Triazenes.** The 1,3-Bis(4'-tolyl)-triazene (V), 1,3-bis(3',4'-dimethylphenyl)-triazene (VI), 1,3-bis(3',4',5'-trimethylphenyl)-triazene (X), 1-(3',4'-dimethylphenyl)-3-(4''-tolyl)-triazene (XI), and 1-(3',4'-dimethylphenyl)-3-phenyltriazene (XII) were prepared by methods described previously [1,13,14]. For the triazene X:

Found %: C 76.75, 76.68; H 8.10, 8.21; N 15.04, 15.04.  $C_{18}H_{23}N_3$ . Calculated %: C 76.82; H 8.23; N 14.93.

**Rearrangement of Triazenes to Orthoaminoazo Compounds.** To a melt of 20 g of the aromatic amine containing 1.25 g of the hydrochloride of the same amine, 10 g of the triazene was added. The mixture was stirred 3 hr at 35°, 3 hr at 40-45°, 3 hr at 50-60°, and 1 hr at 70°. The precipitate of the azo dye was filtered off and washed with alcohol. The pure material was obtained by recrystallization from alcohol.

The results of the rearrangement of the triazenes to orthoaminoazo compounds are presented in the table.

**Rearrangement of 1,3-Bis(3',4'-dimethylphenyl)-triazene (VI). In Aniline Medium.** After carrying out the rearrangement and separation of the 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV), the aniline was steam-distilled from the mother liquor (pH of medium = 8). A 10 g quantity of a dark red gummy material was recovered from the residue. By fractional crystallization from alcohol, 4-aminoazobenzene (VII) and 3,4-dimethyl-4'-aminoazobenzene (VIII) were obtained.

**In p-Toluidine Medium.** As a result of the rearrangement, 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV) was obtained. A 2.65 g quantity of this substance (m.p. 169-170°) was hydrogenated in 30 ml of alcohol in the presence of 2 g of skeletal nickel catalyst for 2 hr at 60 atm and 70-90°. After removal of the catalyst, the solvent was distilled off (pH of medium = 2), the residue was made alkaline to pH 9-10, and by steam distillation 0.5 g (39.4%) of 3,4-dimethylaminobenzene was obtained with mp. 47-48°, giving no melting point depression in a mixed sample with known material. From the residue after distilling off the 3,4-dimethylaminobenzene, there was filtered off 1.21 g (85%) of 4,5-diamino-1,2-xylene with m.p. 126-127°, giving no melting point depression in a mixed sample with known material.

**In Chlorobenzene.** A 5 g quantity of (VI) was subjected to rearrangement in 10 ml of chlorobenzene and 0.5 ml of concentrated hydrochloric acid, obtaining 2.1 g (42%) of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV). In the same medium, but in the presence of 1 g of 3,4-dimethylaminobenzene hydrochloride instead of hydrochloric acid, compound (IV) was obtained with a yield of 2.5 g (50%).

**Rearrangement of 1-(3',4'-Dimethylphenyl)-3-(4''-tolyl)-triazene (XI). In Aniline Medium.** Obtained 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (IV). A 0.7 g quantity of (IV) was hydrogenated and treated as described above; obtained 0.16 g (47.8%) of 3,4-dimethylaminobenzene with m.p. 47-48° and 0.2 (53%) of 4,5-diamino-1,2-xylene with m.p. 126-127°, giving no melting point depression in mixed samples with known materials.

## SUMMARY

1. The rearrangement of symmetrical triazenes in a medium of an aromatic amine that is more highly ring-alkylated than are the triazene components leads to orthoaminoazo compounds with their electrophilic and nucleophilic components corresponding structurally to the amine of the medium.
2. A synthesis has been accomplished for orthoaminoazo compounds that do not correspond in molecular structure to the structure of the initial triazene components.
3. Data have been presented to show that the aminoazo rearrangement of triazenes is an intramolecular reaction.

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SYNTHESIS OF 2,6-DIMETHYL-2-CYANO-5-(p-METHOXYPHENYL)-CYCLOHEXANOL-1

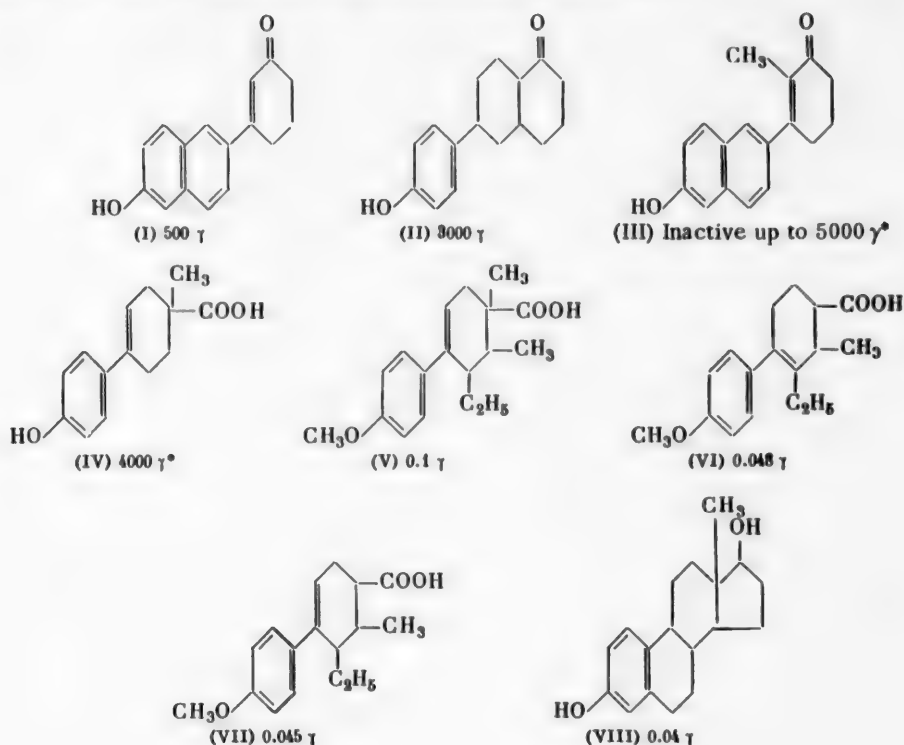
G. V. Kondrat'eva, L. F. Kudryavtseva, and S. I. Zav'yalov

N. D. Zelinskii Institute of Organic Chemistry,  
Academy of Sciences, USSR

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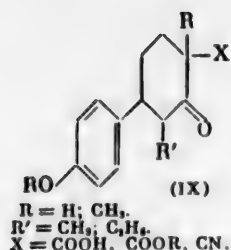
In recent years syntheses have been accomplished for a whole series of bi- and tricyclic structural analogs of steroid hormones (I-VII), many of which possess marked estrogenic activity [1-5].



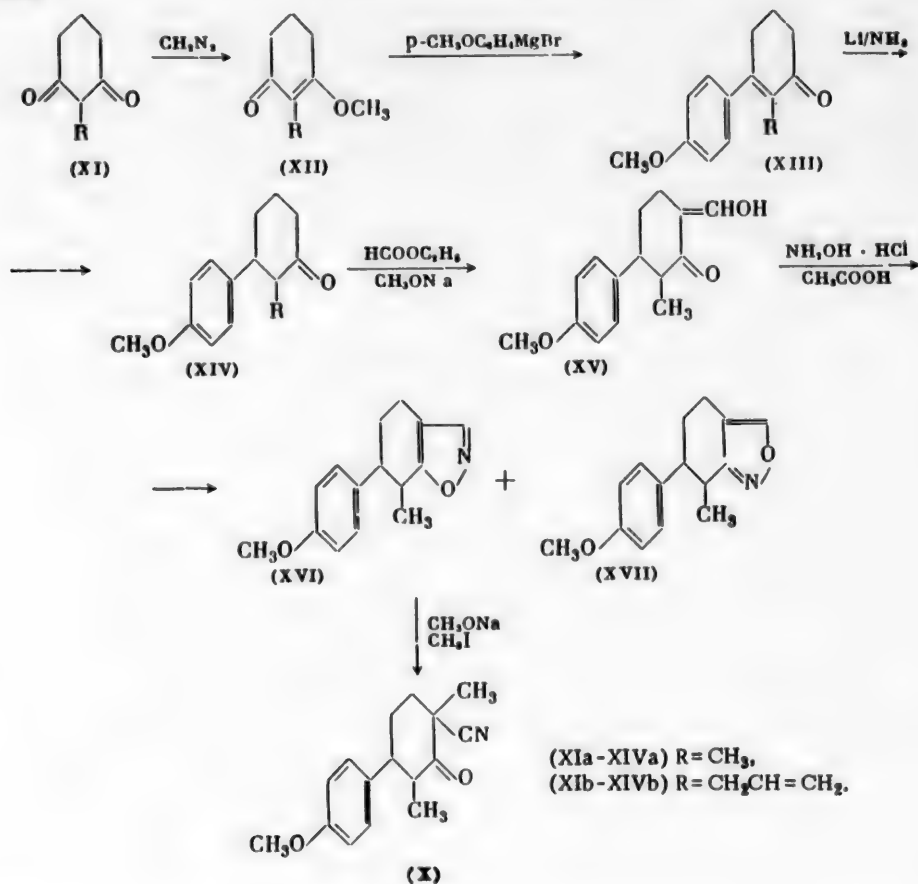
The physiological action of the 2-methyl-3-ethyl-4-(p-methoxyphenyl)-cyclohexenecarboxylic acids (VI) and (VII) is almost equal to the action of estradiol (VIII), which is one of the most potent natural estrogens.

For an investigation of the relationship between hormonal activity and structure in a series of seco-steroids, it is necessary to locate sufficiently general and practical schemes of synthesis of steroid analogs. In this connection, compounds of the type of (IX), are of great interest as intermediates; owing to the great variety of substituents, they can be converted not only to analogs of doisyolic acid, but also to substances close to estrone in structure [6].

\*According to the data of I. A. Eskin and M. P. Danilova.

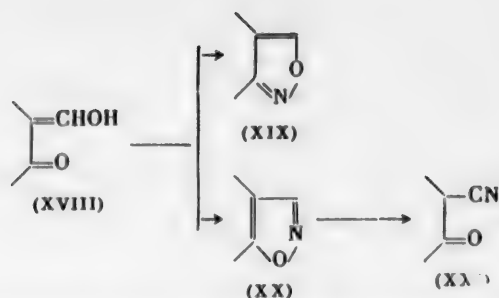


In the present work, a synthesis is described for one of the representatives of this type of compounds, 2,6-dimethyl-2-cyano-5-(p-methoxyphenyl)-cyclohexanone-1 (X) from methyldihydroresorcinol (XIa) according to the following scheme:



The methyl ether of the enol of methyldihydroresorcinol (XIa) was brought into a Grignard reaction with p-methoxyphenylmagnesium bromide; the resulting unsaturated ketone (XIIIa) was then reduced to 2-methyl-3-(p-methoxyphenyl)-cyclohexanone-1 (XIVa) by lithium in liquid ammonia. Varying the substituents in the dihydroresorcinol molecule, it is possible to obtain ketones of the type of (XIII) and (XIV) with various alkyl groups in the 2-position. By a Claisen condensation of the saturated ketone (XIVa) with formic ester in the presence of sodium methoxide, 2-methyl-6-hydroxymethylene-3-(p-methoxyphenyl)-cyclohexanone-1 (XV) was obtained; this was treated (without recovery in the pure form) with hydroxylamine hydrochloride.

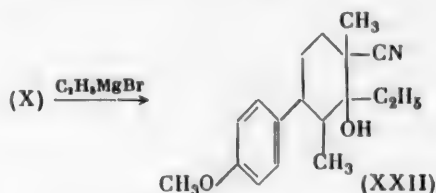
The formation of the isoxazoles (XIX) and (XX) on the interaction of hydroxymethyleneketones (XVIII) with hydroxylamine [7] and the phenomenon of isomerization in the series of isoxazoles [8] has been known for many years.



Taking advantage of the differing behavior of the isomeric isoxazoles toward sodium methoxide [9, 10], one of these forms (XX) can be converted successfully to the corresponding ketonitrile (XXI), and the other isomer (XIX) can thereby be recovered in the pure form.

After the reaction of the hydroxymethyleneketone (XV) with hydroxylamine hydrochloride in acetic acid, a mixture of the two isomeric isoxazoles (XVI) and (XVII) was obtained; this mixture, without further purification, was subjected to treatment with sodium methoxide and methyl iodide, recovering 2,6-dimethyl-2-cyano-5-(p-methoxyphenyl)-cyclohexanone-1 (X) and the isoxazole (XVII). The use of potassium *t*-butoxide in *t*-butanol instead of sodium methoxide leads to analogous results.

The structure of the ketonitrile (X) was confirmed by the UV spectrum of its 2,4-dinitrophenylhydrazone and by a Grignard reaction with ethylmagnesium bromide, which gave 1-ethyl-2,6-dimethyl-2-cyano-5-(p-methoxyphenyl)-cyclohexanol-1 (XXII).



## EXPERIMENTAL PART

**Interaction of Methyl Ether of Enol of Methylidihydroresorcinol (XIIa) with p-Methoxyphenylmagnesium Bromide.** A solution of 11 g of the enol ether (XIIa) in 60 ml ether was added at 0° to a Grignard reagent prepared from 3.4 g magnesium and 29.2 g p-bromoanisole in 100 ml absolute ether. The mixture was stirred 3 hr at 20° and allowed to stand overnight at this temperature. Then 100 g ice and 100 ml of 10% hydrochloric acid were added, and the mixture was heated 1 hr at 34° and then cooled; the ether layer was separated, and the aqueous layer was extracted three times with ether. The combined ether extract was washed twice with dilute sodium carbonate solution (to remove traces of methylidihydroresorcinol and dried with magnesium sulfate; after removal of the ether, the residue was vacuum distilled. Obtained 12.1 g of a very viscous oil with b.p. 142-150° (1 mm), which crystallized completely in several days. After freezing at -70°, from ether solution there was recovered 10 g (60%) of 2-methyl-3-(p-methoxyphenyl)-2-cyclohexenone-1 (XIIIa) in the form of white crystals, m.p. 62-63° (from heptane).

Found %: C 77.85; 77.84; H 7.45, 7.46. C<sub>14</sub>H<sub>16</sub>O<sub>2</sub>. Calculated %: C 77.74; H 7.45.

2,4-Dinitrophenylhydrazone—dark red crystals, m.p. 203-204° (from methanol).

Found %: C 60.34; 60.47; H 5.09, 5.07; N 14.40, 14.11. C<sub>20</sub>H<sub>20</sub>O<sub>5</sub>N<sub>4</sub>. Calculated %: C 60.59; H 5.08; N 14.13.

Semicarbazone—light yellow crystals, m.p. 232-233° (from mixture of methanol and dioxane).

Found %: C 66.12, 66.06; H 6.80, 6.81; N 15.51, 15.59. C<sub>15</sub>H<sub>16</sub>O<sub>2</sub>N<sub>3</sub>. Calculated %: C 65.91; H 7.00; N 15.37.

**Reduction of 2-Methyl-3-(p-methoxyphenyl)-2-cyclohexenone-1 (XIIIa) by Lithium in Liquid Ammonia.** To a solution of 1 g lithium in 500 ml liquid ammonia, there was added 5 g of the unsaturated ketone (XIIIa) in a mixture of 70 ml absolute ether and 70 ml anhydrous dioxane. After 15-min stirring, anhydrous ammonium chloride was added until the reaction mixture was decolorized. The contents of the flask were poured into 500 ml cold water, and

the solution was extracted three times with ether. The combined ether extract was dried with magnesium sulfate, and, after removal of the ether, the residue was vacuum distilled. Obtained 4 g (80%) of 2-methyl-3-(p-methoxyphenyl)-cyclohexanone-1 (XIVa) in the form of a colorless oil with b.p. 140-141° (1 mm),  $n_D^{21}$  1.5410.

Found %: C 76.97, 76.80; H 8.43, 8.33.  $C_{14}H_{18}O_2$ . Calculated %: C 77.01; H 8.30.

2,4-Dinitrophenylhydrazone—orange crystals, m.p. 197-199° (from mixture of alcohol, dioxane, and ethyl acetate).

Found %: C 59.71, 59.80; H 5.42, 5.60; N 14.41, 14.24.  $C_{20}H_{22}O_5N_4$ . Calculated %: C 60.29; H 5.56; N 14.06.

Synthesis of 2-Allyl-3-(p-methoxyphenyl)-2-cyclohexenone-1 (XIIIb). On treating 20 g of allyldihydroresorcinol (XIb) with excess ether solution of diazomethane, there was obtained 14.4 g of the enol ether (XIIIb) in the form of an oil with b.p. 105-113° (4 mm),  $n_D^{17.5}$  1.5325, which was used without further purification for the Grignard reaction.

Under the conditions described for the unsaturated ketone (XIIIa), from 14.4 g of the enol ether (XIIIb) and a Grignard reagent prepared from 4.2 g magnesium and 36.5 g bromoanisole in 100 ml ether, there was obtained 13.8 g of an oil. On freezing an ether solution of this oil at -70°, 1.75 g of crystals was recovered (not studied further), and from the mother liquor there was obtained 9 g (40%) of 2-allyl-3-(p-methoxyphenyl)-2-cyclohexenone-1 (XIIIb) in the form of a colorless oil with b.p. 150-151° (1.5 mm),  $n_D^{21.5}$  1.5825.

Found %: C 78.92, 78.90; H 7.32, 7.60.  $C_{16}H_{18}O_2$ . Calculated %: C 79.31; H 7.49.

2,4-Dinitrophenylhydrazone—bright red crystals, m.p. 176-177°.

Found %: N 13.68, 13.61.  $C_{22}H_{22}O_5N_4$ . Calculated %: N 13.26.

Reduction of 2-Allyl-3-(p-Methoxyphenyl)-2-cyclohexenone-1 (XIIIb) by Lithium in Liquid Ammonia. Under the conditions described for the ketone (XIIIa), from 6 g of 2-allyl-3-(p-methoxyphenyl)-2-cyclohexenone-1 (XIIIb), obtained 4.5 g (75%) of the saturated ketone (XIVb) in the form of a colorless oil with b.p. 150° (1.5 mm),  $n_D^{16.5}$  1.5410.

Found %: C 78.80, 78.62; H 8.52, 8.52.  $C_{16}H_{20}O_2$ . Calculated %: C 78.67; H 8.25.

2,4-Dinitrophenylhydrazone—orange crystals, m.p. 129-131°.

Found %: N 13.58, 13.64.  $C_{22}H_{24}O_5N_4$ . Calculated %: N 13.21.

Formylation of 2-Methyl-3-(p-methoxyphenyl)-cyclohexanone-1 (XIVa). To a suspension of sodium methoxide (from 2.8 g sodium) in 50 ml anhydrous benzene, 12 g of formic ester and 8.7 g of the ketone (XIVa) were added, and the mixture was left overnight at 20°. After treatment with water the benzene layer was separated off and the aqueous layer was extracted with ether and acidified with dilute hydrochloric acid (1:1). The liberated oil was extracted with ether; removal of the ether gave 5.4 g of the hydroxymethyleneketone (XV), which was used in the following stage without additional purification.

Interaction of 2-Methyl-6-hydroxymethylene-3-(p-methoxyphenyl)-cyclohexanone-1 (XV) with Hydroxylamine. A solution of 5.2 g of the hydroxymethyleneketone (XV) in 80 ml glacial acetic acid was stirred vigorously for 8 hr at 78° with 2.9 g powdered hydroxylamine hydrochloride. After removal of the acetic acid under vacuum, the residue was treated with water and extracted with ether, recovering 4.1 g of a semicrystalline mass—a mixture of the isomeric isoxazoles (XVI) and (XVII).

Preparation of 2,6-Dimethyl-2-Cyano-5-(p-methoxyphenyl)-cyclohexanone-1 (X). To 6.5 g of the mixture of isoxazoles (XVI) and (XVII) in 30 ml benzene, there was added a solution of sodium methoxide (from 0.9 g sodium and 30 ml methanol). After 30 min standing at 20° and 10 min refluxing, the mixture was cooled, and methyl iodide was added, first 6 ml, and then (in 1 hr) 4 ml. The reaction mass was left 2 hr at 20°, and then refluxed 4 hr. After removal of the solvents under vacuum, the residue was extracted with benzene. The benzene solution was washed with a 5% potassium hydroxide solution and with water and dried with magnesium sulfate. From the oil remaining after distilling off the benzene by freezing at -70° in ether solution, 1.8 g of the isoxazole was obtained (XVII) in the form of white crystals with m.p. 161-162° (from methanol).

Found %: C 73.52, 73.77; H 7.45, 7.48; N 5.47, 5.38.  $C_{15}H_{17}O_2N$ . Calculated %: C 73.74; H 7.42; N 5.73.

From the mother liquor, recovered 2.2 g of the ketonitrile (X) in the form of a colorless oil with b.p. 150-154° (2 mm),  $n_D^{20}$  1.5458.

Found %: N 5.17, 5.40.  $C_{16}H_{19}O_2N$ . Calculated %: N 5.44.

2,4-Dinitrophenylhydrazone—m.p. 200-201°,  $\lambda_{\max}$  365 m $\mu$  (alcohol).

Found %: N 15.71, 15.60.  $C_{22}H_{23}O_2N_5$ . Calculated %: N 16.02.

**Interaction of the Ketonitrile (X) with Ethylmagnesium Bromide.** To a solution of 2 g of the ketonitrile (X) in 15 ml ether, there was added at -70° a Grignard reagent obtained from 0.23 g magnesium and 2 g ethyl bromide. At 20° the mixture was acidified with dilute hydrochloric acid (1:1), the ether layer was separated off, and the aqueous layer was extracted with ether. After removal of the ether, there remained 2 g of an oil, from which by freezing at -70° from a small quantity of dry ether there was recovered 0.26 g of the bicyclic cyanoalcohol (XXII) in the form of white crystals with m.p. 158-159° (from a mixture of benzene and heptane).

Found %: C 75.52, 75.77; H 8.68, 8.63; N 4.89, 4.73.  $C_{19}H_{25}O_2N$ . Calculated %: C 75.24; H 8.73; N 4.88.

#### SUMMARY

The synthesis of 2,6-dimethyl-2-cyano-5-(p-methoxyphenyl)-cyclohexanone-1 has been accomplished; this is a possible intermediate for the preparation of analogs of doisyolic acid and steroid compounds.

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# REACTION OF DEHYDROCHLORINATION OF N- $\beta$ -CHLOROETHYLACETAMIDE

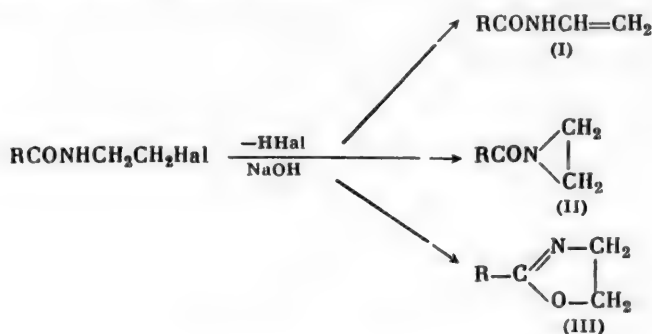
S. S. Skorokhodov, S. G. Ershova, N. V. Mikhailova,  
and A. A. Vansheidt

Institute of High Molecular Weight Compounds,  
Academy of Sciences, USSR

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The synthesis of N-vinyl compounds is of considerable interest, since they are monomers for the preparation of derivatives of polyvinylamine. At present there are known many N-vinylimides of dicarboxylic acids [1], N-vinyl-carbamates [2], and a number of other N-vinyl monomers and their polymers. The possibilities of synthesizing a polyvinylamine through these derivatives are limited either by difficulties in synthesis of the monomers, or by difficulties in carrying out the reactions in the chains of the polymers. These circumstances compel a continuation of the search for new accessible N-vinyl compounds. Among the work of this nature, attention is drawn to the communications of Bacskai and Halmos [3-5] on the synthesis of a series of aliphatic secondary N-vinylamides by dehydrochlorination of the corresponding  $\beta$ -chloroethylamides under mild conditions. The compounds obtained, as indicated by the authors without experimental details, could be polymerized successfully only on acidic catalysts. The data presented have subsequently been cited in the chemical literature [6], even though they evoke doubt from two points of view. On the one hand, Welzel and Greber recently communicated briefly on the synthesis of secondary aliphatic amides by reaction of vinyl isocyanate with Grignard reagents, and polymerization of the amides with the usual radical initiators [7]. On the other hand, the reaction of dehydrochlorination of aliphatic  $\beta$ -haloethylamides under the action of nucleophilic agents can lead to various products.



Moreover, a direct substitution reaction, forming  $\text{RCONHCH}_2\text{CH}_2\text{OH}$ , is also possible. The Hungarian scientists assumed without proof the formation of the compound (I). At the same time, other directions are also possible; the formation of (III) is especially probable, since the available literature data favor the exclusive formation of 2-oxazolines on the dehydrohalogenation of aromatic  $\beta$ -haloethylamides [8]. Unsubstituted 2-oxazoline can be obtained by the dehydrochlorination of  $\beta$ -chloroethylformamide [9]. All of this casts doubt on the very possibility of applying the reaction of dehydrohalogenation of  $\beta$ -haloethyl derivatives for the synthesis of secondary N-vinyl compounds, since one cannot exclude participation of the reactive  $\beta$ -amide group.

We selected the reaction of dehydrochlorination of  $\beta$ -chloroethylacetamide as the object of investigation. The synthesis of the initial chloride and the final stage were carried out according to the scheme and under the conditions of Bacskai and Halmos [4]. The reaction product is a mobile, colorless liquid, boiling at 108-109°. The absence of



high-boiling products allows one to exclude from consideration the product of direct substitution,  $\beta$ -hydroxyethyl-acetamide. Thus, it is necessary to make a choice among the structures of N-vinylacetamide (I,  $R=CH_3$ ), N-acetyl-ethyleneimine (II,  $R=CH_3$ ), and 2-methyl-2-oxazoline (III,  $R=CH_3$ ). Of these compounds, (I) has not been described; (II) has been synthesized by the action of ketone on ethyleneimine. The properties of (II) were not described, except the boiling point under vacuum and a tendency toward spontaneous polymerization in the course of 1-2 days [10]; (III) is stable and has been known for many years [11].

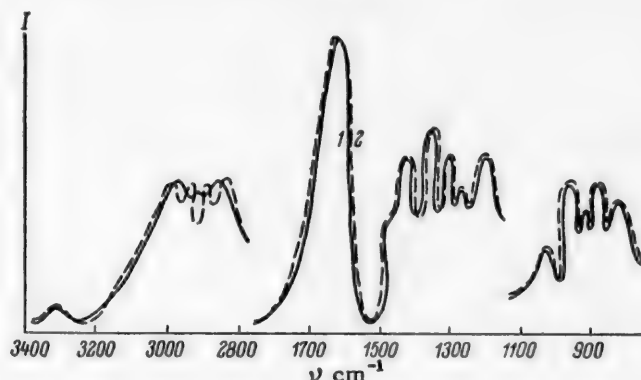


Fig. 1. Absorption curves: 1) Known 2-methyl-2-oxazoline (III); 2) product of dehydrochlorination reaction.

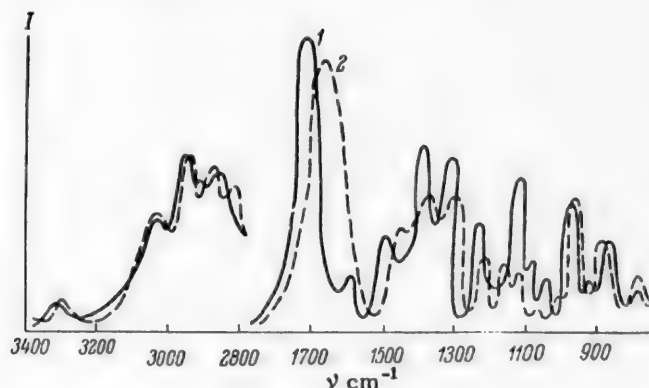


Fig. 2. Absorption curves: 1) N-acetyleneimine (II); 2) product of isomerization of (II).

The constants of the product that we obtained under the conditions of Bacskai and Halmos agreed with the constants of (III), and a mixed sample of the picrates of the reaction product and of a known synthesized (III) did not show any melting point depression [12]. We synthesized (II) by the action of acetyl chloride on ethyleneimine; it proved to be unstable and darkened rapidly in storage; since the necessary data were absent in the literature [10], it was characterized completely.

For final proof, considering in particular the possibility of isomerization of (II) to (III), we took infrared absorption spectra of the reaction product and of known compounds in the interval  $2.5\text{--}13.0\ \mu$ . It should be emphasized that there are no data in the literature on the vibrational spectra of N-acyl- or N-aroylethyleneimines nor of 2-alkyl-2-oxazolines.

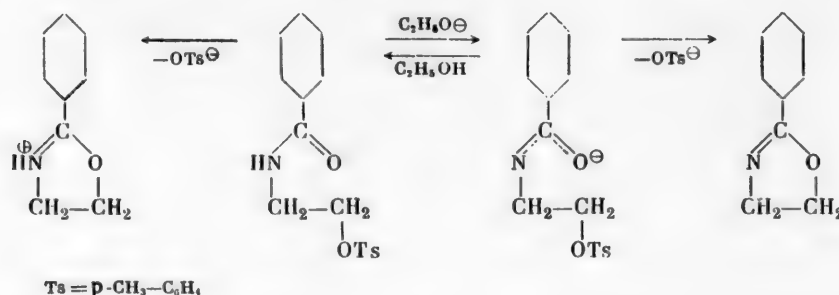
Absorption bands of the N-H and C=C bands are absent from the curves (Fig. 1), as is the so-called amide-H band in the  $1500\text{--}1550\text{ cm}^{-1}$  region [14]. These data are evidence against the structure (I). The intense band at  $1678\text{ cm}^{-1}$  can be treated on the basis of data on Raman spectra of aliphatic iminoethers, having an intense band near  $1670\text{ cm}^{-1}$  that is characteristic for the C=N bond in the N=C-O grouping [15]. The contours of the curves for the reaction product and for (III) coincide. In the spectrum of (II) (Fig. 2) an intense band is observed at  $1704\text{ cm}^{-1}$ , which can be attributed to the C=O bond.

The contour of the curve is different from the contour of the curves of the reaction product and of (III). A direct determination of the ethyleneimine ring based on the deformation band near  $800\text{ cm}^{-1}$  is apparently impossible because of disturbance of the specificity on introducing substituents on the nitrogen [13].

Thus, the spectral analysis favors the structure (III). The low-intensity absorption bands at  $3335$  and  $1642\text{ cm}^{-1}$  which are also observed in the Raman spectra that we measured can be attributed to the unassociated N-H bond and to the C=C bond, and attest to an insignificant amount of admixture of N-vinylacetamide.

The observation that the main direction of the reaction is toward the formation of the oxazoline can be explained on the basis of the work of Winstein [16], Heine [8, 17], who studied the kinetics of formation of 2-phenyl-2-oxazoline in the methanolysis of  $\beta$ -bromoethylbenzamide, and other authors.

On the basis of the broad experimental material of Winstein, a general scheme has been proposed for processes of similar type.



Such processes of intramolecular cyclization connected with the participation of a neighboring  $\beta$ -amino group (so-called "anchimerical participation") [18] in the dehydrohalogenation reaction have been observed in the aromatic series, but apparently they are also possible in the aliphatic series, in spite of the lesser protonization of the amide hydrogen.

We carried out the reaction of dehydrochlorination of  $\beta$ -chloroethylacetamide by sodium methoxide in methanol, i.e., under the most favorable conditions for forming an oxazoline, and recovered that compound (III). The hypothesis of the formation of (II) with its subsequent isomerization to (III) (for example, in the process of distillation) was eliminated by taking the spectrum of a hexane solution of the reaction product before distillation. Only (III) was detected. In an attempt at distillation of (II) at normal pressure, the greater part of the substance was polymerized, and only a small quantity of (III) was distilled over, as demonstrated by taking the infrared spectrum. A case of a similar thermal isomerization has been observed in the conversion of N-benzoyl ethyleneimine to 2-phenyl-2-oxazoline [19]. At the same time, the thermal isomerization of the aliphatic 2,2-dimethyl-N-acetyleneimine leads almost quantitatively to the corresponding methallylacetamide [20].

We have also observed the isomerization of (II) to (III) by the action of a saturated alcoholic solution of picric acid on (II). The picrate that was precipitated did not give any melting point depression with the picrate of known (III). This case can be explained on the basis of the work of Winstein who showed that for example, benzamidoethyl tosylate is isomerized quantitatively in alcoholic solution at  $25^\circ$ , forming the oxazoline ion [16]. Apparently in our case also the picric acid readily opens the unstable imide ring, and the ester that is formed is isomerized rapidly to the oxazoline derivative.

#### EXPERIMENTAL PART

N- $\beta$ -Hydroxyethylacetamide was synthesized with 87.5% yield [4]. B.p.  $158-160^\circ$  at 3 mm,  $n_D^{25}$  1.4709.

N- $\beta$ -Chloroethylacetamide was obtained with yield 64.5% [4]. Dioxane was used as the solvent instead of benzene.

B.p.  $100-101^\circ$  (3 mm),  $n_D^{20}$  1.4740,  $d_4^{20}$  1.1630,  $MR_D$  29.38; calc. 29.40.

Found %: Cl 29.25, 29.47.  $C_4H_9ONCl$ . Calculated %: Cl 29.20.

Dehydrochlorination of N- $\beta$ -Chloroethylacetamide. a) To a suspension of 20.0 g of powdered NaOH in 100 ml of hexane, with vigorous stirring and heating to  $70^\circ$ , 44.3 g of the chloride was dropped in over a 1.5 hr period. After

1.5 hr, an additional 5.0 g of NaOH was added, and stirring was continued another 1.5 hr. After removing the sediment, the hexane solution was distilled. Obtained 15.55 g (50.5%) of product.

B.p. 108-109°,  $n_D^{20}$  1.4330,  $d_4^{20}$  1.0128,  $MR_D$  22.05; calc. 22.06.\*  
Found %: N 16.42.  $C_4H_7ON$ . Calculated %: N 16.46.

The picrate was obtained by combining alcoholic solutions of the reaction product and picric acid in the cold. M.p. 164-166° (from isopropanol). A mixed sample with the picrate of (III) did not give any melting point depression.

The infrared spectrum was measured in a 0.012-mm layer in  $CCl_4$  solution and in vapors on an infrared spectrometer of IVS and IKS-14 construction, in LiF and NaCl prisms. The Raman spectrum was measured in a quartz spectrograph ISP-51 with photoelectric recording.

$\Delta\nu$ : 1680 (10), 1631 (2), 1467 (6), 1448 (4), 1395 (1), 1363 (1), 1229 (1), 1205 (2), 1172 (1), 1044 (2), 1034 (2), 989 (4), 940 (4), 903 (4), 654 (7), 592 (2).

The reaction proceeded analogously on using benzene instead of hexane. Yield 50.0%.

b) A 6.5 g quantity of sodium was dissolved in 100 ml of methanol; 29.78 g of the chloride was dropped in rapidly with stirring, and the mixture was stirred 1 hr longer. The insoluble NaCl was filtered off and washed with methanol. Distillation gave 7.9 g of the product, at 107-108°. Yield 30.0%.

B.p. 107-108°,  $n_D^{20}$  1.4330,  $d_4^{20}$  1.0075,  $MR_D$  21.97; calc. 22.06.

The picrate was prepared as indicated above; m.p. 164-166°. A mixed sample with the picrate of (III) did not give any melting point depression. The infrared spectrum was identical with the spectrum of (III).

2-Methyl-2-oxazoline (III). Obtained 2.7 g of (III) with  $n_D^{20}$  1.4337. Yield 9.0% [12]. M.p. of picrate 165-167° (from ethanol). Literature data: 163° [12], 167-169° [22].

N-Acetyleneimine (II). To a solution of 7.16 g of ethyleneimine and 16.83 g of freshly distilled triethylamine in 40 ml of anhydrous benzene, with vigorous stirring and cooling to 7-8°, there was dropped in slowly a solution of 11.8 ml of freshly distilled acetyl chloride in 10 ml of anhydrous benzene. The reaction proceeded violently, with immediate precipitation of a white sediment of triethylamine hydrochloride. After completion of the dropping, stirring was continued 0.5 hr. The sediment was removed and washed with two 20 ml portions of benzene. The residue after distilling off the benzene was vacuum distilled. Obtained 3.68 g of (II). Yield 30.0%.

B.p. 38-39° (17 mm),  $n_D^{20}$  1.4378,  $d_4^{20}$  0.9923,  $MR_D$  22.43; calc. 22.09.

Found %: C 56.25; 56.50; H 8.25, 8.19; N 16.87, 16.76.  $C_4H_7ON$ . Calculated %: C 56.45; H 8.29; N 16.46.

Isomerization of (II) to (III). a) In an attempt to distil 2.06 g of (II) at normal pressure and a temperature of 150°, there was recovered 0.1 g of stable product with  $n_D^{20}$  1.4345. The spectrum was identical with the spectrum of (III).

b) By the action of a saturated alcoholic solution of picric acid on (II), yellow crystals were precipitated, melting at 164-166° after recrystallization from isopropanol. A mixed sample with the picrate of known (III) did not give any melting point depression.

## SUMMARY

1. It has been shown that the dehydrochlorination of N- $\beta$ -chloroethylacetamide by NaOH under mild conditions gives 2-methyl-2-oxazoline.

2. It has been shown that the data of Bacskai and Halmos on the synthesis of N-vinylacetamide (I) and also, apparently, of other aliphatic N-vinylamides, are erroneous, and the polymers they obtained do not represent derivatives of polyvinylamine.

3. By acetylation of ethyleneimine with acetyl chloride in the presence of triethylamine, N-acetyleneimine has been obtained, and it has been shown that it is partially isomerized to 2-methyl-2-oxazoline on heating to 150° or by the action of a saturated alcoholic picric acid solution.

\* In the calculation the value of atomic refraction for nitrogen was taken equal to 3.05, corresponding to nitrogen in the grouping H-C=N in iminoethers [21].

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# ON THE ABSORPTION SPECTRA OF DIMEROCYANINES, DERIVATIVES OF IMIDAZOLIDINONE (4)

## I. THE ABSORPTION SPECTRA IN THE VISIBLE REGION

M. V. Deichmeister, N. S. Spasokukotskii,

Yu. Sh. Moshkovskii and L. D. Zhilina

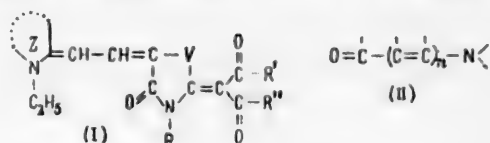
The All-Union Scientific Research Institute of Motion Picture Photography

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 11,

pp. 3631-3637, November, 1961

Original article submitted July 28, 1960

Dimerocyanines, derivatives of imidazolidinone (4), of the general structure (I) are related to the internally ionized polymethine dyes and contain two chromophoric systems of the amide type (II) [1].



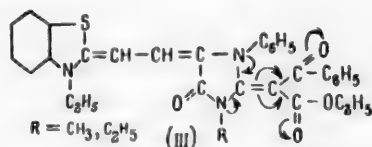
R, R' = alkyl and aryl,

R'' = aryl, ethoxy, or phenylamino group,

V = N-R,

Z = the residue of the nitrogen containing heterocyclic ring.

Similar dye derivatives of thiazolidinone (4) (I; V = S) were described earlier [2-4]. However, their optical properties were not investigated in detail. According to the available data they do not differ from the well-known merocyanines which contain one chromophoric system of type (II) [1].\* On investigation of the absorption spectra of the synthesized dimerocyanines—the derivatives of 1-phenyl-3-alkylimidazolidinone (4) of structure (III) with residues of ethyl benzoylacetate, and also of dyes with benzoylacetone and ethyl acetoacetate residues—in alcohol, it was found that these compounds differ sharply among themselves both in the position of the absorption maximum and also in the shape of the absorption curve and its dependence on the nature of the alkyl group (CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>) in the 3-position of the imidazolidinone residue (Figs. 3 and 4, curve 2). Substituents on the nitrogen atom of the heterocyclic residues ordinarily have little influence on the color of polymethine dyes. The only exceptions are the non-planar cyanines, for which cases there is observed a displacement of the absorption maximum when the alkyl group on the nitrogen atoms of the heterocyclic residues is made heavier; the net result of the change of shape of the absorption curves is to somewhat decrease its broadening [6, 7].



\* We obtained the series of dimerocyanines, derivatives of imidazolidinone (4), (I, Z = benzothiazole; V = N-C<sub>6</sub>H<sub>5</sub> or N-CH<sub>3</sub>; R = CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>; R' = C<sub>6</sub>H<sub>5</sub>; R'' = CH<sub>3</sub> or OC<sub>2</sub>H<sub>5</sub>) by the condensation of the quaternary salts of 1-phenyl- or 1-methyl-2-methylmercapto-5-(3'-ethylbenzothiazolinyldene-2'-ethylidene)-imidazolidinone (4) (1 g-mole) with the ethyl esters of benzoylacetic or acetoacetic acids or with benzoylacetone (3 g-mole) in propanol in the presence of triethylamine (2 g-mole) at room temperature [5]. The properties of these compounds are cited in Table 2.

For the elucidation of the cause of the change of shape noted in the curves in our case, we measured the absorption spectra of the dimerocyanines (III) in non-polar and polar solvents with different dielectric constants and also in mixtures of these solvents. The absorption spectra were measured on an SF-2 spectrophotometer. All the solvents used were subjected to special purification and dehydration [8-10].

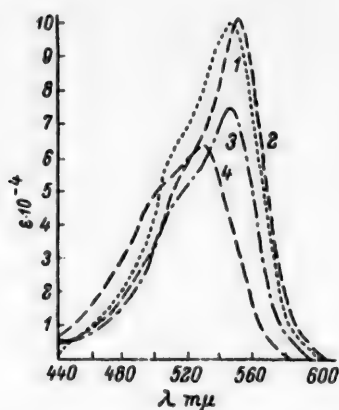


Fig. 1. The absorption spectra of the dye (III) ( $R=CH_3$ ) in nonpolar solvents. 1)  $C_6H_5Cl$ ; 2)  $C_6H_6$ ; 3)  $CCl_4$ ; 4) cyclo- $C_6H_{12}$ .

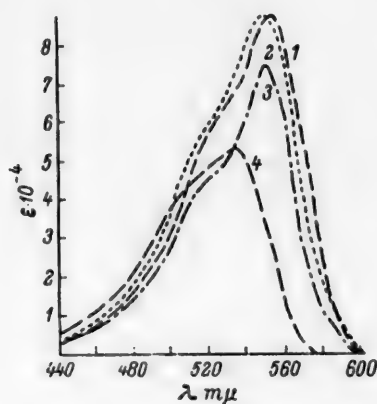


Fig. 3. The absorption spectra of the dye (III) ( $R=CH_3$ ) in alcohols. 1)  $CH_3OH$ ; 2)  $C_2H_5OH$ ; 3)  $n-C_3H_7OH$ ; 4)  $n-C_4H_9OH$ ; 5)  $n-C_{10}H_{21}OH$ .

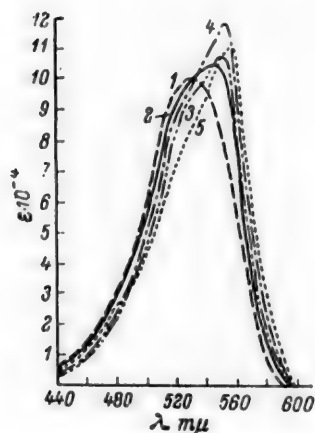


Fig. 2. The absorption spectra of the dye (III) ( $R=C_2H_5$ ) in non-polar solvents. 1)  $C_6H_5Cl$ ; 2)  $C_6H_6$ ; 3)  $CCl_4$ ; 4) cyclo- $C_6H_{12}$ .

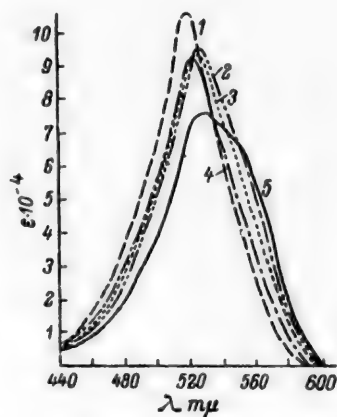


Fig. 4. The absorption spectra of the dye (III) ( $R=C_2H_5$ ) in alcohols. 1)  $CH_3OH$ ; 2)  $C_2H_5OH$ ; 3)  $n-C_3H_7OH$ ; 4)  $n-C_4H_9OH$ ; 5)  $n-C_{10}H_{21}OH$ .

A  $1 \times 10^{-4}$  M solution (2.5 ml) of the dye in methanol was evaporated in vacuo to dryness, and to the residue was added 5 ml of the required solvent from a burette. In this way  $0.5 \times 10^{-5}$  M solutions were obtained. Solutions in previously prepared mixtures of benzene and methanol were obtained in an analogous fashion.

The results are given in Figs. 1-4 and also in Table 1.

As is apparent from the data, the absorption spectra of both dyes in non-polar solvents contain two bands—an intense long wave-length band with a shoulder on the short wave-length side. As the dielectric constant of the solvent is lowered both absorption bands are displaced to the short wave-length region, the intensity of the first decreasing at the same time as the intensity of the second increases; this becomes especially noticeable in cyclohexane



(Figs. 1 and 2, curve 4). The absorption spectra of the 3-methyl and 3-ethyl derivatives differ sharply in aliphatic alcohols (Figs. 3 and 4). A broad band with a blunt maximum at 530 m $\mu$  is observed for the case of the methyl derivative in methanol solution. The lowering of the dielectric constant of the alcohols together with the bathochromic movement of the absorption maximum causes a sharp change in the shape of the curve. A long wave-length band with a shoulder on the short wave-length side appears. It should be observed that the intensity of the first band is increased while that of the shoulder is decreased on changing from ethanol to decyl alcohol. In the case of the 3-ethyl derivative (Fig. 4) there is a short wave-length maximum in methanol solution, while the long wave-length band becomes noticeable only in decyl alcohol, and its intensity does not exceed the short wave-length maximum.

TABLE 1

The solvent R	Polar Solvents					Nonpolar Solvents			
	CH <sub>3</sub> OH	C <sub>2</sub> H <sub>5</sub> OH	n-C <sub>3</sub> H <sub>7</sub> OH	n-C <sub>4</sub> H <sub>9</sub> OH	n-C <sub>10</sub> H <sub>21</sub> OH	C <sub>6</sub> H <sub>5</sub> Cl	C <sub>6</sub> H <sub>6</sub>	CCl <sub>4</sub>	cy-C <sub>6</sub> H <sub>11</sub>
DK	31.2	25.8	22.2	19.2	< 3.5	5.53	2.28	2.2	2.05
CH <sub>3</sub>	—	546	550	552	554	553	549	547	531
	530	(~ 520)	(~ 520)	(~ 520)	(~ 520)	(~ 520)	(~ 520)	(~ 515)	(~ 510)
C <sub>2</sub> H <sub>5</sub>	—	—	—	—	(~ 550)	556	554	552	535
	521	524	525	526	530	(~ 520)	(~ 520)	(~ 520)	(~ 510)

As is apparent from the data of Table 1 (the position of the inflection on the absorption curve is given in parentheses), when the dielectric constant of the solvent is lowered there is an initial bathochromic movement of the absorption maxima of both bands followed by a gradual deepening of the color, from which it may be concluded that the structure of these dyes in alcohol solution is closer to the internally ionized form.

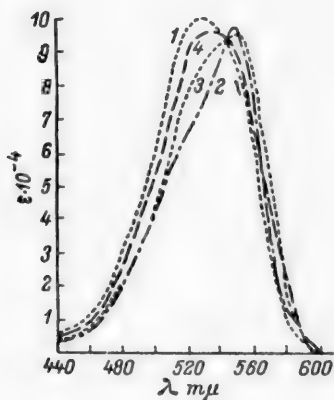


Fig. 5. The absorption spectra of the dye (III) (R=CH<sub>3</sub>) in mixtures of benzene and methanol. 1) Methanol; 2) benzene; 3) 50% methanol; 4) 80% methanol.

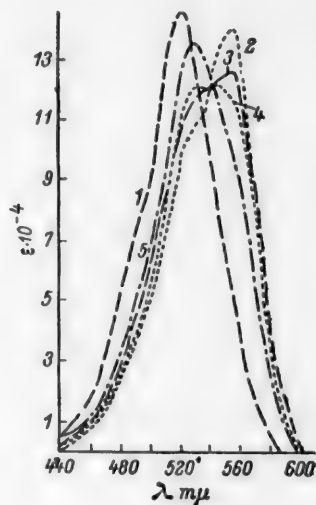


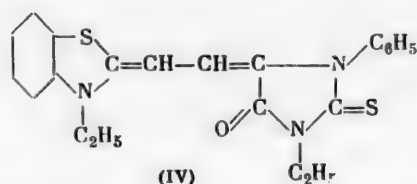
Fig. 6. The absorption spectra of the dye (III) (R=C<sub>2</sub>H<sub>5</sub>) in mixtures of benzene and methanol. 1) Methanol; 2) benzene; 3) 3% methanol; 4) 5% methanol; and 5) 25% methanol.

One could propose that the anomaly which is indicated above in the absorption spectra of the dyes being investigated is explained by an interaction of the dye and the alcohol molecules, the formation of solvate complexes with the ethylate being especially strong (compare [11, 12]). The absorption spectra of the dimerocyanines (III) were

measured in mixtures of benzene and methanol in order to test the correctness of this suggestion. As is apparent from Figs. 5 and 6, the addition of methanol to a benzene solution of the dye causes a change in the shape of the absorption curve which sets in at about 5% (10.4 mole %) in the case of the 3-ethyl derivative (Fig. 6, curve 4), but which becomes significant only for a 50% (68.9 mole %) solution of methanol in benzene for the 3-methyl substituted compounds (Fig. 5, curve 3). In both cases these changes occur gradually and the curve passes through an isobestic point demonstrating the presence of two forms of the dye—solvated and unsolvated.

It should be observed that an analogous phenomenon is observed when anhydrous acetic acid is added to a benzene solution of the dye, and that the phenomenon is more apparent in the case of the dimerocyanines containing a benzoylacetone residue. These data confirm the suggestion made above of the possibility of formation of solvated forms of these dyes.

The appearance of these complexes in the presence of methanol or acetic acid probably occurs as a result of the formation of hydrogen bonds between the carbonyl oxygen of the ethyl benzoylacetate residue and the active hydrogen atom of the solvating molecule (the alcohol or acid). This is confirmed by the fact that the addition of methanol to a benzene solution of the dimethine merocyanine (IV) causes only a gradual deepening of the color without a change of shape of the absorption curve.



The formation of a hydrogen bond with the solvent in the case of the dye (III) is more probable the greater the negative charge on the oxygen atom of the carbonyl groups of the ethyl benzoylacetate residue, this charge arising as a result of the displacement of the electron density from the nitrogen atoms of the imidazolidinone residue. The degree of electron displacement and therefore also the magnitude of the negative charge on the oxygen atom is obviously connected not only with the basicity of this residue but also with the geometric configuration of the molecule of the dye.

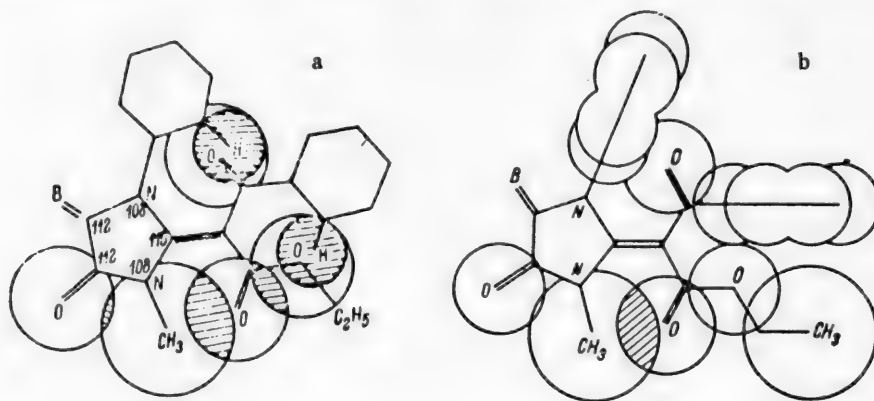
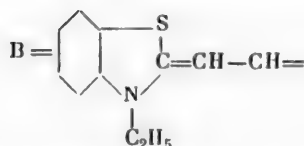


Fig. 7. Projections of three-dimensional models of the dye (III) ( $R = CH_3$ );



a) co-planar; b) with the phenyl groups rotated perpendicularly to the plane of the molecule.

As is apparent from the spacial models of the dye (III) ( $R = CH_3$ ), which are pictured in Figs. 7a and 7b, there is for this compound considerable steric hindrance to the arrangement of the whole molecule in a single plane. The

TABLE 2.

R	R'	R''	R'''	Yield %	External appearance and solvent for crystallization	M.p.	Molecular formula	% N	
								Found	Calc.
CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	47	Dark-red needles with green luster (ethanol)	223—224°	C <sub>27</sub> H <sub>27</sub> O <sub>4</sub> N <sub>3</sub> S	6.60 *	6.54 *
CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	30	Red-violet needles (benzene)	239—241	C <sub>28</sub> H <sub>29</sub> O <sub>4</sub> N <sub>3</sub> S	8.44, 8.34	8.34
C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	50.9	Red-violet needles (isoamyl alcohol)	259—260	C <sub>32</sub> H <sub>29</sub> O <sub>4</sub> N <sub>3</sub> S	5.78, 6.09 *	5.81 *
C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	62	Violet needles (isoamyl alcohol)	231—232	C <sub>33</sub> H <sub>31</sub> O <sub>4</sub> N <sub>3</sub> S	5.51, 5.50 *	5.66 *
C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	42.9	Red-violet needles (benzene + benzine, 2:1)	220—222	C <sub>27</sub> H <sub>27</sub> O <sub>4</sub> N <sub>3</sub> S	8.69, 8.75	8.58
C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	22	Red-violet needles (benzene)	179—180	C <sub>28</sub> H <sub>29</sub> O <sub>4</sub> N <sub>3</sub> S	7.74, 7.64	7.85
C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	14.9	Dark-blue needles (benzene)	224—225	C <sub>32</sub> H <sub>29</sub> O <sub>4</sub> N <sub>3</sub> S	7.70	7.84

\* Sulfur.

ethyl benzoylacetate residue is obviously out of the plane of the imidazolidinone ring—even to a greater degree in the case of the 3-ethyl derivatives (because of the larger volume of the ethyl group as compared with the methyl). This escape from the plane by means of rotation around the carbon-carbon bond of the ethyl benzoylacetate residue with the heterocyclic ring favors electronic displacement, which in the given case leads to a decrease of the degree of double-bondedness. Thus an increase in the volume of the substituent in the 3-position of the dimerocyanine (III) must promote an increase of the charge on the oxygen atom of the carbonyl group and, consequently, also the formation of the solvated form of the dye.

We measured the absorption spectra of the dimerocyanine derivatives of thiazolidinone (4), (I; V = S, R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, R' = C<sub>6</sub>H<sub>5</sub>, R'' = OC<sub>2</sub>H<sub>5</sub>) and of 1-methyl-3-alkylimidazolidinone (4) (I, V = N-CH<sub>3</sub>; R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, R' = C<sub>6</sub>H<sub>5</sub>, R'' = OC<sub>2</sub>H<sub>5</sub>), the molecules of which were also incompletely co-planar.

In neither case was a change of shape of the absorption curves observed when methanol was added to benzene solutions of the dyes. In the first case, the color of the dye gradually deepened, while in the second it initially deepened (to 10%—19.8 M % methanol), and then the absorption maxima began to be displaced toward the short wave-length region. Thus there occurs initially an adjustment of the electron density in the chromophore, and later the structure of the dye becomes closer to the internally ionized form for dyes which are derivatives of 1-methyl-3-alkylimidazolidinone (4) as well as those of the compound (III).

These data indicate that the appearance of two equilibrated forms of the dye is connected not only with the steric hindrance to co-planar positioning of the molecule but also with the presence in the 1-position of the imidazolidinone residue of a phenyl group (the dye III). Its role is as yet insufficiently clear, although it might be suggested that it comes down to a screening of the carbonyl groups from the solvent molecules. From this point of view an increase of the volume of the substituent in the 3-position of the imidazolidinone residue which leads to a greater discursion of the ethyl benzoylacetate residue from the plane will decrease the screening effect of the phenyl group and consequently ease solvation.

It is possible that this question will be answered with greater clarity as a result of the investigation which we have begun of the absorption spectra of these dyes in the ultra-violet and infra-red regions.

## SUMMARY

1. Measurements were made (in various solvents and mixtures of the absorption spectra in the visible region of the

dimerocyanines, derivatives of imidazolidinone (4), which contain residues of benzoylacetone, ethyl benzoylacetate, and ethyl acetoacetate in the 2-position.

2. The similarity of the absorption spectra of the dimerocyanine derivatives of 1-phenyl-3-methyl- and 1-phenyl-3-ethylimidazolidinone (4) in non-polar solvents was established, as well as their sharp difference in alcoholic solvents caused by the presence of an equilibrium between two forms of the dye due to solvation of the carbonyl group of the ethyl benzoylacetate residues.

3. It was shown that the solvation process was dependent on the presence of steric hindrances to a co-planar positioning of the ethyl benzoylacetate residue with the remainder of the molecule and also on the presence of a phenyl group in the 1-position of the imidazolidinone nucleus.

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# THE CYANOETHYLATION OF ANILINE WITH 8-SUBSTITUTED PROPIONITRILES

P. F. Butskus and R. Yu. Stonite



### The Vil'nyuso State University

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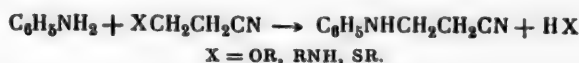
The present article is a continuation of work on the cyanoethylation of aromatic amines by  $\beta$ -substituted propionitriles [1-4].

Decyanoethylated compounds	β-phenylamino-propionitrile •	
	yield (%)	the m.p. found ••
$(\text{CH}_3)_2\text{CH}-\text{O}-\text{CH}_2\text{CH}_2\text{CN}$	9.5	50°
$\text{CH}_2=\text{CHCH}_2-\text{O}-\text{CH}_2\text{CH}_2\text{CN}$	9.2	49—50
$\text{CH}_3(\text{CH}_2)_4\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2\text{CN}$	9.2	47.5
$\text{CH}_3(\text{CH}_2)_6\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2\text{CN}$	10.9	49.5
$\text{CH}_3(\text{CH}_2)_8\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2\text{CN}$	11.6	49.5
$\text{CH}_3\text{OCH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2\text{CN}$	27.4	49—50
$\text{C}_2\text{H}_5\text{OCH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2\text{CN}$	27.4	49—50
$\text{CH}_3\text{OCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2\text{CN}$	24.7	49—50
$\text{O}(\text{CH}_2\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_2\text{CN})_2$	35.1	50
$\text{C}_2\text{H}_5\text{NH}-\text{CH}_2\text{CH}_2\text{CN}$	60.2	48—49
$\text{HOCH}_2\text{CH}_2\text{NH}-\text{CH}_2\text{CH}_2\text{CN}$	64.3	48—49
$\text{HOCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$	53.0	48.5
$(\text{HOCH}_2\text{CH}_2)_3\text{N}-\text{CH}_2\text{CH}_2\text{CN}$	60.2	48—49
$\text{C}_6\text{H}_5\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2\text{CN})_2$	55.6	48.5
 $\text{N}-\text{CH}_2\text{CH}_2-\text{CN}$	70.2	48
 $\text{N}-\text{CH}_2\text{CH}_2\text{CN}$	70.2	48
$\text{CH}_3-\text{S}-\text{CH}_2\text{CH}_2\text{CN}$	10.0	48.5
$\text{HOCH}_2\text{CH}_2-\text{S}-\text{CH}_2\text{CH}_2\text{CN}$	9.2	48.5
$\text{C}_6\text{H}_5-\text{S}-\text{CH}_2\text{CH}_2\text{CN}$	9.2	48.5

\*Data from the literature: m.p. 49-50° [5].

\* \* Test mixtures of the products of transcyanoethylation with a known sample of  $\beta$ -phenylaminopropionitrile which was obtained by the action of acrylonitrile on aniline showed no depression of the melting point.

The cyanoethylation of aniline by  $\beta$ -substituted propionitriles goes according to the following scheme.



The following cyanoethylating agents were used: the product of the monocyanoethylation of isopropyl, allyl, hexyl, octyl, and decyl alcohols, the mono-methyl and mono-ethyl ethers of glycol, the mono-methyl ether of diethyleneglycol, ethylamine, ethanolamine, diethanolamine, pyrrolidine, morpholine, methyl mercaptan, 2-mercapto-

ethanol, phenyl mercaptan, and also the products of the dicyanoethylation of diethylene glycol, ethanolamine, and benzylamine. The product of this reaction is in all cases the product of transcyanoethylation- $\beta$ -phenylaminopropionitrile.

#### EXPERIMENTAL PART

A mixture of 0.02 g-moles of the  $\beta$ -substituted propionitrile and 0.1 g-moles of aniline was refluxed in 150 ml of water for 20 hrs. The reaction mixture was evaporated in vacuo to dryness on a water bath, 50 ml of water was added, and the mixture was again evaporated to dryness. The residue ( $\beta$ -phenylaminopropionitrile) was recrystallized from aqueous alcohol. The results of the experiments are given in the table.

The reaction of aniline with N-cyanoethylated compounds was carried out in the presence of 1.85 ml of concentrated hydrochloric acid, and the reaction with  $\beta$ -alkoxypropionitriles in the presence of a small quantity of sodium hydroxide (0.025 g) or of triethylamine (0.3 g). The reaction with S-cyanoethylated compounds occurred without a catalyst.

#### SUMMARY

The process of transcyanoethylation takes place by the interaction of aniline with  $\beta$ -substituted propionitriles and forms  $\beta$ -phenylaminopropionitrile.

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## p-ANISIDINE AS AN AGENT FOR DECYANOETHYLATION

P. F. Butskus and N. V. Raguotene

The Vil'nyus State University

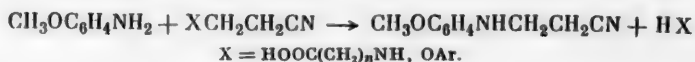
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It has been shown in the preceding communications that by the action of aniline on some cyanoethylated compound there are formed the products of decyanoethylation and transcyanoethylation [1-4].

The results of a study of the interaction of p-anisidine with N-cyanoethylated  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\epsilon$ -amino acids, and also with the  $\beta$ -cyanoethyl ethers of phenols are reported in the present work. The results of this reaction are in all cases the products of decyanoethylation—the corresponding amino acids and phenols. The reaction according to the following scheme.



The amino acids are also obtained by the action of p-anisidine on the esters, amides, and hydrazides of the N-cyanoethylated  $\alpha$ -amino acids, since hydrolysis of the esters, amides, and hydrazides occurs simultaneously with the decyanoethylation.

The product of transcyanoethylation—N-( $\beta$ -cyanoethyl)-p-anisidine—may be isolated from the reaction mixtures in addition to the product of the decyanoethylation.

Only the starting materials could be isolated when attempts were made to carry out this reaction of p-anisidine under the same conditions with compounds cyanoethylated on a carbon atom, for example: 1,1,1-tri-( $\beta$ -cyanoethyl)-acetone, 2,2,6,6-tetra-( $\beta$ -cyanoethyl)-cyclohexanone, 1,1,1-tri-( $\beta$ -cyanoethyl)-acetophenone,  $\beta$ -indolyl- $\beta$ -propionitrile, etc.

### EXPERIMENTAL PART

The reaction of p-anisidine with N-cyanoethylated  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\epsilon$ -amino acids, and with the esters, amides, and hydrazides of N-cyanoethylated  $\alpha$ -amino acids. A mixture of 0.02 g-moles of the cyanoethylated compound and 0.1 g-mole of p-anisidine was refluxed with 150 ml of water for 20 hrs. The reaction mixture was filtered after cooling and the filtrate was evaporated to a small volume. The residual aromatic amine was removed by extraction with ether. The product of decyanoethylation was precipitated by the addition of alcohol (sometimes a mixture of alcohol and ether) to the aqueous solution. The results of the experiments are given in the table.

The reaction of p-anisidine with  $\beta$ -cyanoethyl ethers of phenols. A mixture of 0.02 g-moles of the  $\beta$ -cyanoethyl ether of a phenol and 0.1 g-moles of p-anisidine was refluxed with 150 ml of water for 20 hrs. Concentrated hydrochloric acid was added to the cooled reaction mixture in order to dissolve the p-anisidine and the product of transcyanoethylation, and the mixture was filtered. The precipitate was dissolved in aqueous alkali, and the solution was filtered. The phenol was precipitated by the addition of concentrated hydrochloric acid to the filtrate (the phenol was sometimes more conveniently isolated by ether extraction directly from the reaction mixture after the addition of the hydrochloric acid). The results of the experiments are given in the table.

### SUMMARY

The process of decyanoethylation (the removal of the  $\beta$ -cyanoethyl group) with the formation of the corresponding amino acids and phenols occurs by the interaction of p-anisidine with N-cyanoethylated  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and

Decyanoethylated compound	The product of decyanoethylation			
	Name	Yield (%)	Melting point	
			Found *	Data from the literature
N-cyanoethylglycocol	Glycocol	90.6	233-235° (dec.)	232-236° (dec.) [5]
N,N-Dicyanoethylglycocol	Ditto	74.6	231-232 (dec.)	
N-Cyanoethyl- $\alpha$ -alanine	$\alpha$ -alanine	74.7	294-295 (dec.)	295 (dec.) [6]
N,N-Dicyanoethyl- $\alpha$ -alanine	Ditto	62.9	290-292 (dec.)	
N-Cyanoethyl- $\alpha$ -aminobutyric acid	$\alpha$ -aminobutyric acid	85.9	284-285 (dec.)	285 (dec.) [7]
N,N-Dicyanoethyl- $\alpha$ -aminobutyric acid	Ditto	80.1	283-284 (dec.)	
N-Cyanoethylvaline	Valine	71.8	295-297 (dec.)	298 (dec.) [7]
N,N-Dicyanoethylvaline	Ditto	60.7	295-296 (dec.)	
N-Cyanoethylleucine	Leucine	73.2	290-291 (dec.)	293-295 (dec.) [7]
N-Cyanoethylisoleucine	Isoleucine	76.3	278-280 (dec.)	280 (dec.) [7]
N-Cyanoethyl- $\beta$ -alanine	$\beta$ -alanine	66.3	196-197 (dec.)	197 (dec.) [8]
N,N-Dicyanoethyl- $\beta$ -alanine	Ditto	60.1	195-196 (dec.)	
N-Cyanoethyl- $\beta$ -phenyl- $\beta$ -alanine	$\beta$ -phenyl- $\beta$ -alanine	75.7	131 (dec.)	131 (dec.) [9]
N-Cyanoethyltaurine	Taurine	75.2	305-310 (dec.)	305-310 (dec.) [10]
N,N-Dicyanoethyltaurine	Ditto	54.0	305-310 (dec.)	
N-Cyanoethyl- $\gamma$ -aminobutyric acid	$\gamma$ -aminobutyric acid	75.7	201-203 (dec.)	203 (dec.) [11]
N-Cyanoethyl- $\epsilon$ -aminocaproic acid	$\epsilon$ -aminocaproic acid	83.9	201-203	
N,N-Dicyanoethyl- $\epsilon$ -aminocaproic acid	Ditto	76.3	200-201	202-203 [7]
The methyl ester of N-cyanoethylglycocol	Glycocol	76.6	230-233 (dec.)	
The methyl ester of N,N-dicyanoethylglycocol	Ditto	73.3	230-233 (dec.)	232-236 (dec.) [5]
The ethyl ester of N-cyanoethylglycocol	Ditto	71.3	231-234 (dec.)	
The ethyl ester of N,N-dicyanoethylglycocol	Ditto	68.6	229-231 (dec.)	
The ethyl ester of N-cyanoethyl- $\alpha$ -alanine	$\alpha$ -alanine	70.2	293-294 (dec.)	295 (dec.) [6]

Decyanoethylated compound	The product of decyanoethylation			
	Name	Yield (%)	Melting point	
			Found*	Data from the literature
The amide of N-cyanoethylglycocoll	Glycocoll	78.6	233-235 (dec.)	232-236 (dec.) [5]
The amide of N,N-dicyanoethylglycocoll	Ditto	81.3	232-234 (dec.)	
The amide of N-cyanoethyl- $\alpha$ -alanine	$\alpha$ -alanine	70.2	293-294 (dec.)	295 (dec.) [6]
The hydrazide of N-cyanoethylglycocoll	Glycocoll	78.6	233-235 (dec.)	232-236 (dec.) [5]
The hydrazide of N-cyanoethyl- $\alpha$ -alanine	$\alpha$ -alanine	66.3	294-295 (dec.)	295 (dec.) [6]
$\beta$ -phenoxypyrronitrile	Phenol	53.2	39-40	42-43 [12]
$\beta$ -Cyanoethyl ether of $\alpha$ -naphthol	$\alpha$ -Naphthol	65.9	96 (sublimes)	96 (sublimes) [13]
$\beta$ -Cyanoethyl ether of $\beta$ -naphthol	$\beta$ -Naphthol	60.8	122-123	122-123 [13]
Di- $\beta$ -cyanoethyl ether of pyrocatechol	Pyrocatechol	40.9	104	104-105 [14]
Di- $\beta$ -cyanoethyl ether of resorcinol	Resorcinol	40.9	109-110	110.7 [14]
Di- $\beta$ -cyanoethyl ether of hydroquinone	Hydroquinone	41.8	170	170.3 [14]

\* Test mixtures of the products of decyanoethylation with the corresponding amino acids gave no depressions of the melting point.

amino acids, with the esters, amides, and hydrazides of N-cyanoethylated  $\alpha$ -amino acids, and also with the  $\beta$ -cyanoethyl ethers of phenols. The product of transcyanoethylation—N-( $\beta$ -cyanoethyl)-p-anisidine—may also be isolated from the reaction mixture.

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# ACETALS OF SIMPLE ETHERS OF HYDROBENZOIN

B. I. Mikhant'ev and L. P. Pavlov

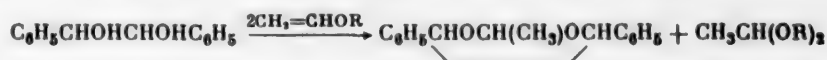
The Voronezh State University

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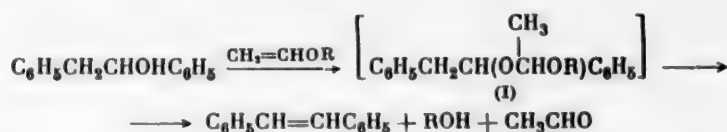
pp. 3643-3646, November, 1961

Original article submitted December 12, 1960

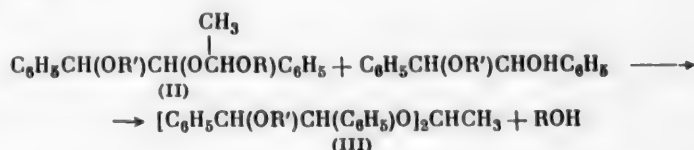
Alcohols easily form acetals by reaction with vinyl alkyl ethers in the presence of acid [1]. Glycols ordinarily [2] give the cyclic acetal, and this is true for both meso- and d,l-hydrobenzoin [3].



The acetalization of  $\alpha$ -hydroxydibenzyl which is similar to hydrobenzoin, proceeds energetically, but the product (I) cannot be purified by vacuum distillation because of the decomposition of the material (above 100° at 2 mm) into stilbene and other compounds.



It therefore appeared interesting to us to attempt to obtain acetals of monoalkyl ethers of hydrobenzoin, the mobile hydrogen of the  $\text{CH}_2$  group of the  $\alpha$ -hydroxydibenzyl being replaced by an alcohol residue which should promote the stability of the substances which are formed. The experiment produced the products (II) and, in addition, the symmetrical acetals (III) which arise together with the saturated alcohol by transesterification of the acetal (II) by the hydrobenzoin monoether.

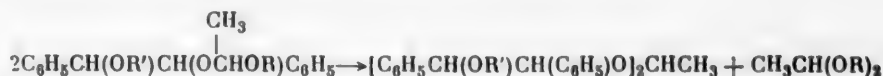


$\text{R} = \text{C}_2\text{H}_5$  and  $\text{C}_4\text{H}_9$ ;  $\text{R}' = \text{CH}_3$  and  $\text{C}_2\text{H}_5$ .

The mechanism of this reaction and the necessity for an acidic medium were confirmed by experiment. In addition, the acid promoted a partial conversion of the alcohol into the dialkylacetal



and an exchange transesterification with symmetrization of the mixed acetal:



The acetals of type (II) which were obtained were colorless, rather viscous liquids; those type (III) were glassy, yellowish substances which were quantitatively decomposed by hydrolysis into acetaldehyde and the original alcohol. Vacuum distillation of the mixed acetal did not cause a noticeable symmetrization.

TABLE 1. The Properties of the Acetals of Simple Ethers of Hydrobenzoin

Substance	Boiling point (pressure in mm)	$d_4^{20}$	$n_D^{20}$	Found			Formula	Calculated				The acetal content as acetalde- hyde (in %) <sup>a</sup>	Yield of orig- inal poly- mer (%)	
				MR <sub>D</sub>	M	%C		%H	MR <sub>D</sub>	M	%C			%H
1-Ethoxy-1-(meso- $\alpha$ -methoxydibenzyl- $\alpha'$ -oxy)-ethylidene acetal	134° (1.5)	1.0430	1.5310	89.11	292.5, 293.4	75.76, 75.89	7.87, 7.91	C <sub>19</sub> H <sub>24</sub> O <sub>3</sub>	87.67	300.4	75.97	8.05	99.04, 98.39	86.9
1-Butoxy-1-(meso- $\alpha$ -methoxydibenzyl- $\alpha'$ -oxy)-ethylidene acetal	159 (1.5)	1.0137	1.5175	98.10	323.8, 315.0	76.65, 76.39	8.48, 8.68	C <sub>21</sub> H <sub>26</sub> O <sub>3</sub>	96.90	328.4	76.79	8.59	97.80, 98.09	91.8
Di-1,1-(meso- $\alpha$ -methoxydibenzyl- $\alpha'$ -oxy)-ethylidene acetal	200-205 (0.3-0.5)	1.1074	1.5697	142.9	461.5, 464.9	79.55, 79.59	7.13, 7.13	C <sub>32</sub> H <sub>34</sub> O <sub>4</sub>	142.1	482.6	79.64	7.10	98.65, 98.30	88.7
1-Ethoxy-1-(meso- $\alpha$ -ethoxydibenzyl- $\alpha'$ -oxy)-ethylidene acetal	148 (1.5)	1.0140	1.5155	93.58	306.3, 305.4	76.43, 76.23	8.17, 8.33	C <sub>20</sub> H <sub>26</sub> O <sub>3</sub>	92.29	314.4	76.40	8.34	98.81, 98.70	88.1
Di-1,1-(meso- $\alpha$ -ethoxydibenzyl- $\alpha'$ -oxy)-ethylidene acetal	203-205 (0.5)	1.0777	1.5540	151.9	504.6, 512.0	79.79, 80.01	7.33, 7.28	C <sub>34</sub> H <sub>38</sub> O <sub>4</sub>	151.4	510.6	79.96	7.50	98.92, 98.53	90.1
Diethyl acetal <sup>a</sup>	103 (758)	0.8261	1.3823	33.31	—	—	—	C <sub>6</sub> H <sub>14</sub> O <sub>2</sub>	33.19	—	—	—	100.59, 100.18	—
Dibutyl acetal <sup>a</sup>	185 (760)	0.8318	1.4090	51.80	—	—	—	C <sub>10</sub> H <sub>22</sub> O <sub>2</sub>	51.67	—	—	—	99.87, 100.46	—

\* Determined by the method of hydrolytic oxime formation.

\*\* In agreement with [1]: B.p. 103-104° (760),  $d_4^{20}$  0.8254,  $n_D^{20}$  1.3820.\*\*\* In agreement with [1]: B.p. 184-185° (760),  $d_4^{20}$  0.8267,  $n_D^{20}$  1.4090.



TABLE 2. Acetalization of Ethers of Hydrobenzoin and  $\alpha$ -Hydroxydibenzyl

Taken		Obtained			Reaction time
The name of the substance	g (ml)	The name of the substance	g	Yield (%)	(in min)
The methyl ether of hydrobenzoin	17.84	Butoxy-(methoxydibenzyl- ethylidene acetal	3.19	16.7	120
Vinyl butyl ether	23.50	Di-(methoxydibenzyl- ethylidene acetal	2.13	15.2	-
Ether (diethyl)	(20)	n-Butyl alcohol*	0.33	-	-
Sulfuric acid (conc.)	0.024	Dibutyl acetal	0.38	-	-
		The methyl ether of hydrobenzoin**	4.55	-	-
The ethyl ether of hydrobenzoin	24.23	Ethoxy-ethoxydibenzyl- ethylidene acetal	4.72	15.0	120
Vinyl ethyl ether	23.10	Di-(ethoxydibenzyl- ethylidene acetal	3.04	11.9	-
Ether	(45)	Ethyl alcohol***	0.21	-	-
Sulfuric acid	0.018	Diethyl acetal	0.56	-	-
$\alpha$ -hydroxydibenzyl	21.00	Stilbene**	5.44	30.0	90
Vinyl butyl ether	33.00	n-Butyl alcohol*	2.84	38.1	-
Ether	(45)	Acetaldehyde****	0.80	18.0	-
Sulfuric acid	0.032	Dibutyl acetal	0.79	4.5	-
		$\alpha$ -hydroxydibenzyl**	1.05	-	-
$\alpha$ -hydroxydibenzyl	5.61	Stilbene**	1.57	34.5	50
Vinyl phenyl ether	6.65	Phenol*****	1.28	53.8	-
Ether	(5)	Acetaldehyde****	0.11	9.9	-
Sulfuric acid	0.011	$\alpha$ -hydroxydibenzyl**	0.60	-	-
The methyl ether of hydrobenzoin	2.28	Di-(methoxydibenzyl- ethylidene acetal	0.80	16.2	120
Butoxy-(methoxydibenzyl- oxy)-ethylidene acetal	3.28	n-Butyl alcohol*	0.12	16.6	-
Ether	(5)	Dibutyl acetal	0.037	4.2	-
Sulfuric acid	0.012	-	-	-	-
Butoxy-(methoxydibenzyl- oxy)-ethylidene acetal	5.00	Di-(methoxydibenzyl- ethylidene acetal	0.10	2.7	120
Ether	(5)	Dibutyl acetal	0.062	4.7	-
Sulfuric acid	0.016	-	-	-	-

\*B.p. 116-117°,  $n_D^{20}$  1.3990; 3,5-dinitrobenzoate m.p. 61-62°; in agreement with [7] m.p. 62.5°.

\*\* Identified by the mixture test.

\*\*\* Calculated as the p-nitrobenzoate with m.p. 56-57° (mixture test).

\*\*\*\* B.p. 17-19°; 2,4-dinitrophenylhydrazones melts at 165-166° (mixture test).

\*\*\*\*\* B.p. 178-179°; 3,5-dinitrobenzoate, m.p. 143-144°; in agreement with [7], m.p. 145-146°.

#### EXPERIMENTAL PART

The methyl (m.p. 100-101°) and ethyl (m.p. 53-54°) ethers of hydrobenzoin used as starting materials were synthesized according to [4], and  $\alpha$ -hydroxydibenzyl-(m.p. 64.5-65.5°) according to [5]. The vinyl ethers were obtained according to [6] and had the following properties: Vinyl ethyl-b.p. 36°,  $n_D^{20}$  1.3774; vinyl butyl-b.p. 93.5-94°,  $n_D^{20}$  1.4030; vinyl phenyl-b.p. 155-156°,  $n_D^{20}$  1.5220.

The reaction of the methyl ether of hydrobenzoin with vinyl ethyl ether. Into a boiling mixture of 22.83 g of the methyl ether of hydrobenzoin, 45 ml of dry ether, and 2 drops of sulfuric acid (0.036 g, d 1.48) was slowly introduced 23.10 g of vinyl ethyl ether, and the mixture was boiled for 2 hrs (from the beginning of the reaction). The

acid was neutralized with 2 g of KOH, and after 12 hrs it was filtered and fractionated in vacuo. Diethyl acetal, 0.85 g, was isolated from the fraction of b.p. 40-70° (10 mm) which had been dried over sodium (12°, 10 hrs). The residue, which was assumed to be the ethylate, was separated from the sodium and converted into ethyl p-nitrobenzoate [7], which was identified by the mixture test. The melting point was 56-57°, the yield 0.77g; calculated as ethanol-0.18 g. The crystals from the fraction which boiled at 120-190° (1.5 mm) were washed with petroleum ether, and after purification were identified by mixed melting point as the methyl ether of hydrobenzoin, 7.12 g. From the filtrate, which was treated with sodium (20°, 48 hrs), there were isolated by fractionation 3.84 g (18.6% of the carbinol which had reacted) of 1-ethoxy-1-(meso- $\alpha$ -methoxydibenzyl- $\alpha'$ -oxy)-ethylidene acetal (Table 1). Several redistillations of the residue yielded di-1,1-(meso- $\alpha$ -methoxydibenzyl- $\alpha'$ -oxy)-ethylidene acetal, 3.18 g (19.2%). A mixture of 3.66 g of the latter and 250 ml of a 0.5 N solution of hydroxylamine hydrochloride in 30% dioxane (for removal of the acetaldehyde) were heated for 40 hrs at 100° in a sealed flask. The methyl ether of hydrobenzoin was separated after partial evaporation and cooling and was confirmed by a mixture melting test. The weight was 3.07 g, m.p. 100-101°. The preparation does not ordinarily require additional purification. Analogous methods were used for the syntheses of the other acetals.

The exothermic reaction of  $\alpha$ -hydroxydibenzyl with vinyl butyl ether (Table 2) gave a light oily acetal which decomposed above 100° (in a vacuum) to a black brittle tar and products of distillation; these were isolated and analyzed. Stilbene was separated from hydroxydibenzyl by distillation and crystallization from alcohol; acetaldehyde was absorbed by cold dibutyl ether, distilled, and converted into the 2,4-dinitrophenylhydrazone. Butyl alcohol and dibutyl acetal were fractionated and quantitatively determined, the first as the 3,5-dinitrobenzoate, the second by its physical constants and by hydrolytic oxime formation [6].

Separate experiments were carried out for the determination of the conditions for the formation of the symmetrical acetals. Butoxy-(methoxydibenzyl)-ethylidene acetal was boiled in ether solution with the methyl ether of hydrobenzoin. Distillation of the mixture showed that butyl alcohol and a little dibutyl acetal (analyzed by hydrolytic oxime formation) were formed only on repetition of the experiment in the presence of sulfuric acid. A certain quantity of dibutyl acetal was obtained by boiling an ether solution of the acetal (II) with acid; the reaction did not occur in the absence of the latter.

#### SUMMARY

1. The stable symmetrical and mixed acetals of simple ethers of hydrobenzoin were obtained.
2. It was established that symmetrization of the acetals of the ethers of hydrobenzoin occurred only in an acidic medium.
3. A scheme for the thermal decomposition of the acetals of  $\alpha$ -hydroxydibenzyl into stilbene, acetaldehyde, and alcohols is proposed.

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# INVESTIGATIONS IN THE FIELD OF SYNTHESIS AND CONVERSIONS OF UNSATURATED ORGANOGERMANIUM COMPOUNDS

## IX. SYNTHESIS AND CONVERSIONS OF PRIMARY AND SECONDARY

### MONOHYDRIC $\gamma$ -GERMANOACETYLENIC ALCOHOLS

I. A. Shikhiev, I. A. Aslanov, and B. G. Yusufov

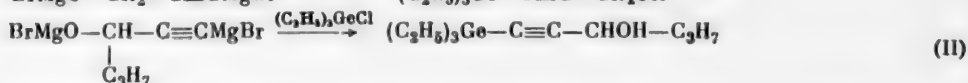
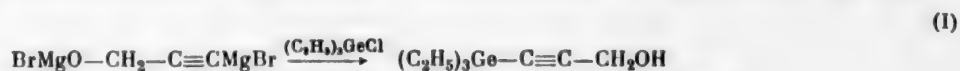
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 11,

pp. 3647-3648, November, 1961

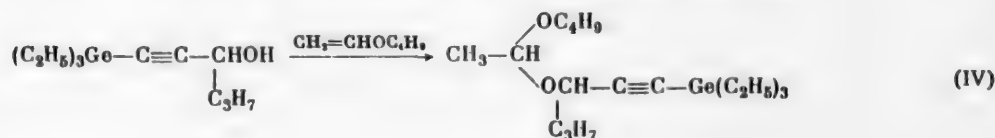
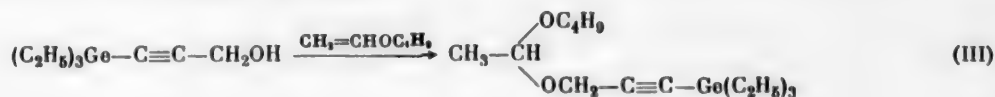
Original article submitted December 27, 1960

In the preceding investigations [1] we studied the interaction of the Iotsich reagent [dimethylethynylcarbinol di(bromomagnesium) salt] with various alkylgermanium bromides. As a result a method was developed for preparing mono-, di-, and trihydric tertiary  $\gamma$ -germanoacetylenic alcohols.

The interaction of the Iotsich reagents, ethynylcarbinol di(bromomagnesium) salt and propylethynylcarbinol di(bromomagnesium) salt, with triethylgermanium chloride was studied in the present work. It was found that the reaction goes toward the formation of primary and secondary  $\gamma$ -germanoacetylenic alcohols according to the scheme.



The presence of hydroxyl groups in the alcohols was proved by preparing the corresponding organogermanium acetylenic acetals [2] from them according to the scheme



## EXPERIMENTAL PART

1-Triethylgermylpropyn-1-ol-3 (I). To the Grignard reagent (prepared from 24 g of magnesium and 109 g of ethyl bromide), 27 g of propargyl alcohol was added with stirring and cooling to  $-3^\circ$ . After stirring for 3 hr 97 g of triethylchlorogermane was added, the reaction mixture being cooled to  $-5^\circ$ , and the latter was left overnight. On the next day the complex was decomposed with water and then dilute hydrochloric acid (5-10%). The ether layer was separated, washed, and dried over sodium sulfate. After distilling twice, 58 g (54%) of the substance was isolated.

One more example of secondary  $\gamma$ -germanoacetylenic alcohols (1-triethylgermylhexyn-1-ol-3) was prepared by an analogous method; its characteristics are given in the table.

n-Butyltriethylgermylpropynylacetal (III). To a mixture of 8 g of 1-triethylgermylpropyn-1-ol-3 and 3 g of vinyl butyl ether, 0.2 ml of 33% hydrochloric acid was added with constant stirring. The reaction-mixture temperature rose to  $38^\circ$  in this case. After this the mixture was heated for 1 hr at  $35-95^\circ$  and then left overnight. On the next

Name	Boiling point (pressure in mm)	$d_4^{20}$	$n_D^{20}$	$M R_p$		Found %:			Molecular formula			Calc. %:		
				found	calc.	C	H	Ge				C	H	Ge
1-Triethylgermylpropyn-1-ol-3	107—108° (4)	1.1100	1.4730	54.86	55.37	50.46	8.52	32.96	$C_{20}H_{18}OGe$			50.31	8.45	33.79
1-Triethylgermylhexyn-1-ol-3	110—111° (2)	1.0106	1.4660	69.10	69.26	55.89	9.24	27.31	$C_{22}H_{20}OGe$			56.09	9.42	28.25
n-Butyltriethylgermylpropynyl- acetal	146—148° (4)	1.1130	1.4519	84.70	85.14	56.98	9.34	22.18	$C_{15}H_{30}O_2Ge$			57.19	9.61	23.04
n-Butyltriethylgermylhexynyl- acetal	152—153° (2)	1.023	1.4600	96.50	99.03	60.76	10.20	19.77	$C_{18}H_{36}O_2Ge$			60.54	10.16	20.33

day the mixture was neutralized with anhydrous potash, the unreacted vinyl ether driven off, and the residue distilled twice. In this case 4.12 g (40%) of the substance was isolated.

One more example of germanoacetylenic acetals (n-butyltriethylgermylhexynylacetal) was prepared similarly; its characteristics are given in the table.

#### SUMMARY

1. The  $\gamma$ -germanoacetylenic alcohols: 1-Triethylgermylpropyn-1-ol-3 and 1-triethylgermylhexyn-1-ol-3, are described for the first time.

2. The germanoacetylenic acetals: n-Butyltriethylgermylpropynylacetal and n-butyltriethylgermylhexynylacetal were prepared and characterized for the first time.

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# INVESTIGATIONS IN THE FIELD OF SYNTHESIS AND CONVERSIONS OF UNSATURATED ORGANOSILICON COMPOUNDS

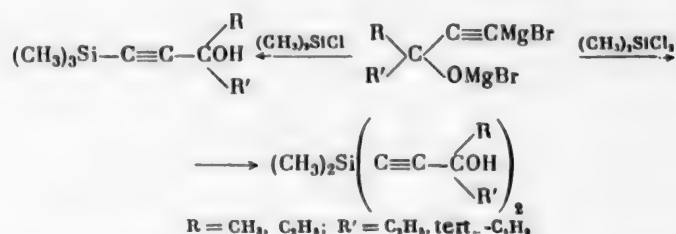
## X. SYNTHESIS OF BRANCHED $\gamma$ -ORGANOSILICON ACETYLENIC ALCOHOLS AND GLYCOLS

I. A. Shikhiev, M. I. Aliev, Sh. V. Gareva,  
and B. M. Guseinzade

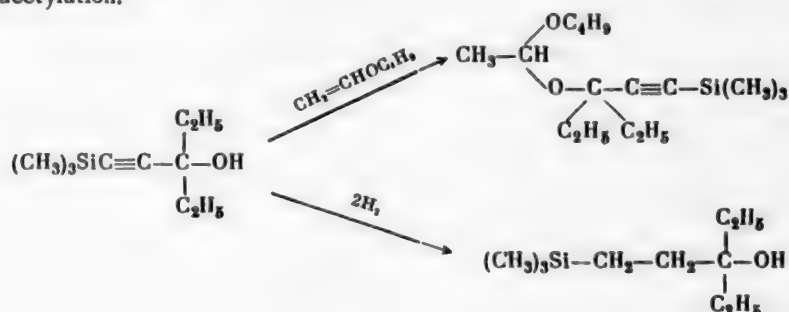
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 11,  
pp. 3649-3652, November, 1961

Original article submitted December 27, 1960

As our investigations showed [1, 2], mono-, di-, and trialkyl-(or -aryl)chlorosilanes react with dimethylethynylcarbinol di(bromomagnesium) salt in the presence of catalytic quantities of cuprous chloride and mercuric chloride to form the corresponding organosilicon acetylenic alcohols and glycols. The present work is a continuation of our investigations.



The structure of the resulting organosilicon acetylenic alcohols and glycols was proved by hydrogenation, acetalization [3, 4], and acetylation.



As a result of the investigation, examples of branched acetylenic and diacetylenic alcohols, glycols, and their derivatives were prepared according to the scheme indicated above and characterized for the first time. The characteristics of all organosilicon compounds obtained are given in the table.

### EXPERIMENTAL PART

**1-Trimethylsilyl-3-ethylpentyn-1-ol-3 (I).** To the Grignard reagent (prepared from 24 g of magnesium and 109 g of ethyl bromide), 56.08 g of diethylethynylcarbinol was added with constant stirring and cooling in ice water [5]. After stirring for 3 hr, the mixture being cooled with ice water, 54 g of trimethylchlorosilane was added. The

Organosilicon Acetylenic Alcohols and their Derivatives

Substance No.	Formulas of organosilicon acetylenic alcohols and their derivatives	Names of compounds	B. p. (pressure in mm)	$d_4^{20}$	$n_D^{20}$	MR <sub>s</sub>		Found %:			Calc. %:		
						found	calc.	C	H	Si	C	H	Si
(I)	$\begin{array}{c} \text{C}_6\text{H}_5 \\   \\ \text{CH}_3-\text{CH}_2-\text{COH}-\text{C}\equiv\text{C}-\text{Si}(\text{CH}_3)_3 \end{array}$	1-Trimethylsilyl-3-ethylpentyn-1-ol-3	69-70° (1.5)	0.8435	1.4459	58.25	58.00	65.42	10.54	14.90	65.14	10.93	15.24
(II)	$\begin{array}{c} \text{OC}_6\text{H}_5 \\   \\ \text{CH}_3-\text{CH}-\text{O}-\text{C}-\text{C}\equiv\text{C}-\text{Si}(\text{CH}_3)_3 \\   \\ \text{C}_6\text{H}_5, \text{C}_6\text{H}_5 \end{array}$	n-Butyl-1-trimethylsilyl-3-ethyl-1-pentynyl-3-acetal	95-96 (1.0)	0.8629	1.4401	86.81	87.77	67.82	11.58	9.34	67.54	11.33	9.87
(III)	$\begin{array}{c} \text{C}_6\text{H}_5 \\   \\ (\text{CH}_3)_2\text{CH}-\text{COH}-\text{C}\equiv\text{C}-\text{Si}(\text{CH}_3)_3 \end{array}$	Bis(3-ethyl-3-hydroxy-pentynyl-1)-dimethylsilane	128-130 (0.5)	0.9254	1.4629	85.22	85.72	68.76	9.96	9.94	68.51	10.06	10.01
(IV)	$\begin{array}{c} \text{C}_6\text{H}_5 \\   \\ (\text{CH}_3)_2\text{CH}-\text{C}-\text{C}\equiv\text{C}-\text{Si}(\text{CH}_3)_3 \\   \\ \text{OCOC}_6\text{H}_5 \end{array}$	Bis(3-ethyl-3-acetoxypentynyl-1)-dimethylsilane	148-149 (2)	0.9650	1.4625	103.84	104.68	65.74	9.33	7.28	65.89	8.85	7.71
(V)	$\begin{array}{c} \text{CH}_3 \\   \\ \text{CH}_3-\text{C}-\text{COH}-\text{C}\equiv\text{C}-\text{Si}(\text{CH}_3)_3 \\   \\ \text{CH}_3 \end{array}$	1-Trimethylsilyl-3,4,4-trimethylpentyn-1-ol-3	64-65 (3)	—	—	—	—	66.81	11.31	12.82	66.59	11.18	14.16
(VI)	$\begin{array}{c} \text{OC}_6\text{H}_5 \\   \\ \text{CH}_3-\text{CH}-\text{O}-\text{C}-\text{C}\equiv\text{C}-\text{Si}(\text{CH}_3)_3 \\   \\ \text{C}_6\text{H}_5 \end{array}$	n-Butyl-1-trimethylsilyl-3,4,4-trimethyl-1-pentynyl-3-acetal	95-97 (2)	0.8598	1.4404	91.56	92.40	67.91	11.54	8.85	68.39	11.47	8.85
(VII)	$\left[ \begin{array}{c} \text{CH}_3 \\   \\ (\text{CH}_3)_2\text{C}-\text{COH}-\text{C}\equiv\text{C}- \end{array} \right]_n \text{Si}(\text{CH}_3)_3$	Bis(3,4,4-trimethyl-3-hydroxypentynyl-1)-dimethylsilane	M.p. 34-65	—	—	—	—	69.64	9.95	8.75	70.07	10.45	9.40



complex was heated and then decomposed with dilute hydrochloric acid (10-15%). The water layer was separated from the ether layer and the latter dried over sodium sulfate. After driving off the ether 37g (40.13%) of (I) was isolated. One more example of branched organosilicon acetylenic alcohols (1-trimethylsilyl-3,4,4-trimethylpentyn-1-ol-3) (V) was prepared similarly; its characteristics are given in the table.

n-Butyl-1-trimethylsilyl-3-ethyl-1-pentynyl-3-acetal (II). To a mixture of 18 g of 1-trimethylsilyl-3-ethylpentyn-1-ol-3 and 10 g of vinyl butyl ether, 0.2 ml of 33% hydrochloric acid was added with stirring. The mixture temperature rose to 31°. The mixture was heated for 40 min at 95° and then left overnight. On the next day it was neutralized with anhydrous potash and distilled twice; 9.42 g (33.11%) of the substance was isolated.

One more example of branched organosilicon acetals (n-butyl-1-trimethylsilyl-3,4,4-trimethyl-1-pentynyl-3-acetal (VI) was prepared similarly; its characteristics are given in the table.

Hydrogenation of 1-Trimethylsilyl-3-ethylpentyn-1-ol-3. A 0.2 g quantity of Raney nickel catalyst in 5 ml of methanol was used. After the mixture was saturated with hydrogen, 0.29 g of (I) was added. A 69.17 ml quantity of hydrogen was absorbed. Theoretically 70.8 ml of hydrogen was required in order to saturate one triple bond.

Bis(3-ethyl-3-hydroxypentynyl-1)-dimethylsilane (III). To the Grignard reagent (prepared from 24 g of magnesium and 110 g of ethyl bromide), 56.08 g of diethylethynylcarbinol was added with constant stirring and cooling in ice water. After stirring for 2 hr, the mixture being cooled with ice water, 34 g of dimethyldichlorosilane was gradually added and the mixture left overnight. On the next day the complex was decomposed with dilute hydrochloric acid (10-15%). The water layer was separated from the ether layer and the latter dried over sodium sulfate. After distilling twice, 32 g (45%) of the substance was isolated. One more example of organosilicon glycols (VII) was prepared similarly; its characteristics are given in the table.

Bis(3-ethyl-3-acetoxypentynyl-1)-dimethylsilane (IV). To 14 g of (III) was added 5.06 g of acetic anhydride. The mixture was heated to 70° for 8 hr and left overnight. On the next day it was distilled twice, 5 g (30%) of the substance being isolated.

#### SUMMARY

1. The following  $\gamma$ -silicon-containing acetylenic alcohols and glycols are described for the first time: 1-Trimethylsilyl-3-ethylpentyn-1-ol-3; 1-trimethylsilyl-3,4,4-trimethylpentyn-1-ol-3; bis(3-ethyl-3-hydroxypentynyl-1)-dimethylsilane; bis(3,4,4-trimethyl-3-hydroxypentynyl-1)-dimethylsilane.

2. The presence of the hydroxyl group in the alcohols and glycols obtained was proved by preparing from them the corresponding organosilicon acetals and acylal: n-Butyl-1-trimethylsilyl-3-ethyl-1-pentynyl-3-acetal, n-butyl-1-trimethylsilyl-3,4,4-trimethyl-1-pentynyl-3-acetal, and bis(3-ethyl-3-acetoxypentynyl-1)-dimethylsilane.

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# PHOSPHORUS-CONTAINING MONOMERS

## I. FULL ESTERS OF VINYLPHOSPHONIC ACID

### WITH VARIOUS FUNCTIONAL GROUPS

M. A. Sokolovskii, P. M. Zavlin, E. L. Geftter,

and P. A. Moshkin

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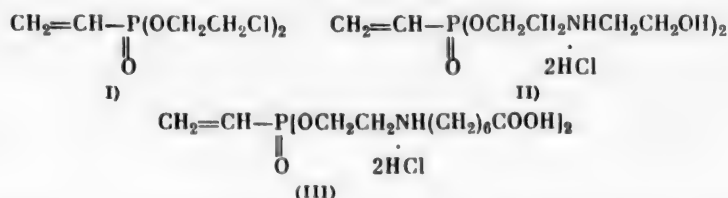
Among the new classes of high-molecular-weight heteroorganic compounds, phosphorus-containing polymers of the most diverse nature have recently begun to attract more and more attention [1]. For the most extreme modification of the properties of the resulting phosphorus-containing polymers, those original phosphorus-containing monomers which would permit the simultaneous or successive occurrence both of polycondensation and polymerization processes in the course of polymer preparation might be of substantial interest.

The present work deals with the synthesis of the first examples of such phosphorus-containing monomers. Certain vinylphosphonic acid derivatives, which if necessary could acquire practical interest depending on their availability, were chosen as the subject of the investigation. Full esters of vinylphosphonic acid, containing paired secondary-amino and carboxyl groups, would be particularly interesting. Di( $\beta$ -chloroethyl) vinylphosphonate (I) could serve as a starting compound for the synthesis of such phosphorus-containing monomers of the indicated structure [2-4].

On synthesizing the monomers the required functional groups may be introduced by means of the Hofmann reaction, through the interaction of di( $\beta$ -chloroethyl) vinylphosphonate with aliphatic amino alcohols and aminocarboxylic acids, respectively [5].

The presence of primary chlorine atoms, a double bond, and ester bonds in the original compound—di( $\beta$ -chloroethyl) vinylphosphonate (I)—makes it necessary to reckon with the possibility of various reactions (occurring separately or in combination): substitution of a chlorine atom, addition to the double bond, and aminolysis.

However, as was shown by an investigation of the reaction in the cases where di( $\beta$ -chloroethyl) vinylphosphonate interacts with ethanolamine and aminoheptanoic acid, respectively, the reaction can be made to go almost exclusively in the first direction under certain conditions, and bis(N- $\beta$ -hydroxyethyl- $\beta$ -aminoethyl) vinylphosphonate (II) and bis(N- $\omega$ -carboxyhexyl- $\beta$ -aminoethyl) vinylphosphonate (III) can be obtained in good yields.



The structures of the phosphorus-containing monomers obtained, contain functional groups which can enter into condensation processes (secondary amino, hydroxyl, carboxyl), and also a vinyl group which makes the polymerization process possible.

Further work in this direction is in progress.

## EXPERIMENTAL PART

Bis(N- $\beta$ -hydroxyethyl- $\beta$ -aminoethyl) Vinylphosphonate (II). Into a three-neck flask, provided with a reflux condenser, thermometer, and dropping funnel, was put 11.6 g (0.05 mole) of di( $\beta$ -chloroethyl) vinylphosphonate (I),

and 6.1 g (0.1 mole) of ethanolamine was added. The mixture was stirred for 1.5-2 hrs at 40-45°, until the reaction was nearly finished, and then heated in a water bath for 1 hr more at 80°. A nearly quantitative yield of bis(N-β-hydroxyethyl-β-aminoethyl) vinylphosphonate dihydrochloride was obtained in this case.

Found %: P 9.0, 9.1; N 7.63; Cl 19.5 (argentometrically).  $C_{10}H_{25}O_5N_2PCl_2$ . Calculated %: P 8.7; N 7.88; Cl 2.00.

A 17.75 g quantity (0.05 mole) of bis(N-β-hydroxyethyl-β-aminoethyl) vinylphosphonate dihydrochloride was added to the ethanolic sodium ethoxide solution obtained by dissolving 2.3 g (0.1 mole) of sodium in 100 ml of absolute ethanol. The precipitated sodium chloride was filtered out and the ethanol distilled off; bis(N-β-hydroxyethyl-β-aminoethyl) vinylphosphonate was obtained in 80% yield.

Found %: P 11.0; N 9.93.  $C_{10}H_{23}O_5N_2P$ . Calculated %: P 10.9; N 10.0.

Bis(N-ω-carboxyhexyl-β-aminoethyl) (Vinylphosphonate (III)). Into a three-neck flask, provided with a reflux condenser, thermometer, and dropping funnel, was put a solution of 11.65 g (0.05 mole) of di(β-chloroethyl) vinylphosphonate (I) in 50 ml of 80% aqueous ethanol, and a solution of 14.5 g (0.1 mole) of ω-aminoheptanoic acid in 50 ml of 80% aqueous alcohol was added. The mixture was heated in a water bath for 4 hr with constant stirring. At the end of the reaction the solvent was distilled off, and bis(N-ω-carboxyhexyl-β-aminoethyl) vinylphosphonate dihydrochloride was obtained in nearly quantitative yield in the form of a glassy, yellow mass.

Found %: P 6.5; N 5.77.  $C_{20}H_{41}O_7N_2PCl_2$ . Calculated %: P 5.93; N 5.35.

A 26.15 g quantity (0.05 mole) of bis(N-ω-carboxyhexyl-β-aminoethyl) vinylphosphonate dihydrochloride was added to the ethanolic sodium ethoxide solution prepared by dissolving 2.3 g (0.1 mole) of sodium in 160 ml of absolute ethanol. The precipitated sodium chloride was filtered out. The ethanol was distilled off. In the residue bis(N-ω-carboxyhexyl-β-aminoethyl) vinylphosphonate was obtained in 80% yield; m.p. 70°.

Found %: P 6.3; N 5.93. M 434 (potentiometric titration).  $C_{20}H_{39}O_7N_2P$ . Calculated %: P 6.88; N 6.2. M 450.

#### SUMMARY

The interaction of di(β-chloroethyl) vinylphosphonate with ethanolamine and ω-aminoheptanoic acid was studied, and bis(N-β-hydroxyethyl-β-aminoethyl) and bis(N-ω-carboxyhexyl-β-aminoethyl) vinylphosphonates, not described earlier, were prepared.

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# SYNTHESIS AND CERTAIN CONVERSIONS OF 2-FURYL-2-THIENYLMETHANE

Ya. L. Gol'dfarb and Ya. L. Danyushevskii

N. D. Zelinskii Institute of Organic Chemistry,  
Academy of Sciences, USSR

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It is well known that di(2-thienyl)methane is an interesting starting compound for the preparation of scarcely-available uni- and bifunctional aliphatic derivatives by reductive sulfurization [1]. Greater possibilities in this respect might arise if an unsymmetrical analog of diphenylmethane were used—2-furyl-2-thienylmethane (FTM) (I), in which specific peculiarities, inherent in the furan and thiophene nuclei, must be manifested. In particular, hydrogenolytic cleavage of the thiophene ring of FTM could give furan derivatives with a long aliphatic chain, whereas acid hydrolysis might give thiophene derivatives.

It seemed that FTM could be prepared most easily through the Kizhner reduction of 2-furyl 2-thienyl ketone [2]. In this case, however, the yield was only 18%. Attempts to synthesize FTM through the condensation of methyl 5-chloromethylfuran-2-carboxylate with thiophene were unsuccessful. Only the condensation of 2-thienyllithium with furfuryl chloride gave FTM in 45-53% yield.

The ultraviolet absorption spectrum\* of FTM in alcohol and heptane (Fig. 1) is characterized by an absorption band in the 2240 Å region ( $\epsilon$  117700); this band is much wider than in the case of furan ( $\lambda_{\max}$  2050 Å,  $\epsilon$  6000 [3];  $\lambda_{\max}$  2080 Å,  $\epsilon$  8000 [4]) or thiophene ( $\lambda_{\max}$  2350 Å,  $\epsilon$  4500 [3];  $\lambda_{\max}$  2300 Å,  $\epsilon$  7080 [5]), which may be explained by superposition of absorption bands characteristic of both of these rings.

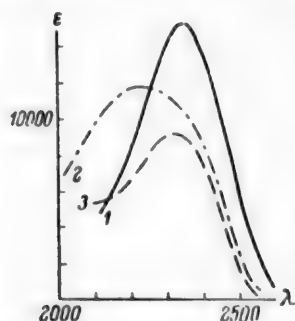


Fig. 1. 1) Di(2-thienyl)methane; 2) 2-furyl-2-thienylmethane; 3) adduct.

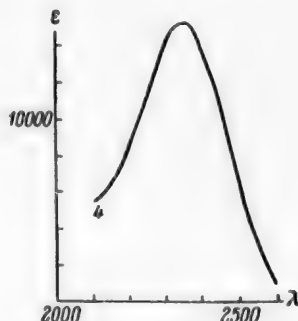


Fig. 2. 2,2-Bis(2-thienyl)butane.

The UV absorption spectrum of FTM sharply differs from that of di(2-thienyl)methane (Fig. 1), which contains a distinct peak ( $\lambda_{\max}$  2360 Å,  $\epsilon$  15300).•• Treatment of FTM with maleic anhydride gives an adduct (II) in which the bond system of the furan ring is changed correspondingly. As should have been expected, the UV absorption spectrum of the adduct corresponds to the thiophene spectrum (Fig. 1):  $\lambda_{\max}$  2320 Å,  $\epsilon$  9200 (in alcohol).

\* The UV absorption spectra were measured by V. A. Petukhov, to whom the authors extend their thanks.

•• The same spectroscopic data ( $\lambda_{\max}$  2360 Å,  $\epsilon$  15300) were obtained for 2,2-bis(2-thienyl)butane in alcohol and heptane (Fig. 2) as for di(2-thienyl)methane.

On the basis of literature data [6] it may be presumed that electrophilic agents will react mainly with the furan ring of FTM, whereas nucleophilic agents, to which some investigators refer organolithium compounds if they react in a homogeneous medium [7], will react mainly with the thiophene ring. In order to test this hypothesis we studied the action of one equivalent of acetic anhydride on an equimolar mixture of furan and thiophene in the presence of boron trifluoride etherate by the method of "competing" reaction. In this case it was found that the acetyl group reacts mainly with the furan ring. The resulting mixture contained 90% of 2-acetylfuran and 10% of 2-acetylthiophene. On metalation of an identical furan-thiophene mixture with one equivalent of butyllithium, practically only the thiophene reacts (carbonation of the metalation product gave thiophene-2-carboxylic acid in 80% yield).

Of the electrophilic substitution reactions of FTM, acetylation by acetic anhydride in the presence of orthophosphoric acid was studied. In this case the monoacetyl derivative of FTM (III) was obtained (yield 40-46%), as well as a little of the diacetyl derivative. The structure of the monoacetyl derivative of FTM (III) (see flow sheet) follows from the fact that its oxidation with potassium ferricyanide gives a mixture of thiophene-2-carboxylic and 5-(2-thenoyl)furan-2-carboxylic (IV) acids. The structure of the latter (IV) was proved by countersynthesis—by condensation of thiophene-2-carbonyl chloride with methyl pyromucate and subsequent hydrolysis of the resulting methyl 5-(2-thenoyl)furan-2-carboxylate (V). This condensation goes with 18-25% yield, which agrees with Gilman's data [8] on the preparation of 5-acetyl- and 5-n-butylfuran-2-carboxylic acid. On oxidation of the monoacetyl derivative (III) with potassium ferricyanide under relatively severe conditions, only thiophene-2-carboxylic acid was isolated.

In searching for ways to prove the structure of ketone (III) a number of experiments were performed, whose results may be of interest in connection with the question of the behavior of the unsubstituted and substituted furylthienyl-methane system toward various oxidizing agents. On oxidation of ketone (III) with sodium hypochlorite the furan ring and methylene bridge persist; 5-(2-thenoyl)furan-2-carboxylic acid (VI) is formed (yield 76%). On the other hand, when 2-methyl-5-(2-furfuryl)-thiophene (VII), synthesized by us, is treated with potassium ferricyanide or potassium permanganate, the furan ring is opened and thiophene-2,5-dicarboxylic acid is formed; this agrees with the observations of certain investigators [9] with regard to the oxidation of substituted furans. However, as we saw above, the furan ring persists to a greater or lesser degree on treatment with potassium ferricyanide under milder conditions (cf. [10]). In conclusion we note that in experiments in the metalation of FTM with phenyl- and butyllithium we have not managed to obtain clear-cut results as yet. The investigation is in progress.

#### EXPERIMENTAL PART

2-Furyl-2-thienylmethane (I). To a solution of 27.7 g (0.33 mole) of thiophene in 120 ml of absolute ether at  $(-3)^{\circ}$  in a nitrogen atmosphere was added 234 ml of a 1.175 N ethereal solution of butyllithium (0.275 mole) during 30 min. After stirring for 30 min at  $(-3)^{\circ}$  and 30 min without cooling, a solution of 29.1 g (0.25 mole) of freshly-distilled furfuryl chloride [11] in 100 ml of absolute ether was gradually added at  $(-3)^{\circ}$ . After 30 min the cooling was stopped; the mixture temperature rose to  $33-34^{\circ}$  and the solution became turbid. When the temperature began to fall, the mixture was kept boiling for 30 min more. One hundred ml of water was cautiously added to the cooled mixture, and the water layer was extracted with ether. The combined ethereal solution was washed with water and dried with calcium chloride. The solvent was driven off, and the residue was distilled twice in vacuo. Yield 21.2 g (51.5%, reckoned on furfuryl chloride).

B.p.  $73-74^{\circ}$  (3.5 mm),  $d_4^{20}$  1.1502,  $n_D^{20}$  1.5568,  $MR_D$  45.95; calc. 46.40.

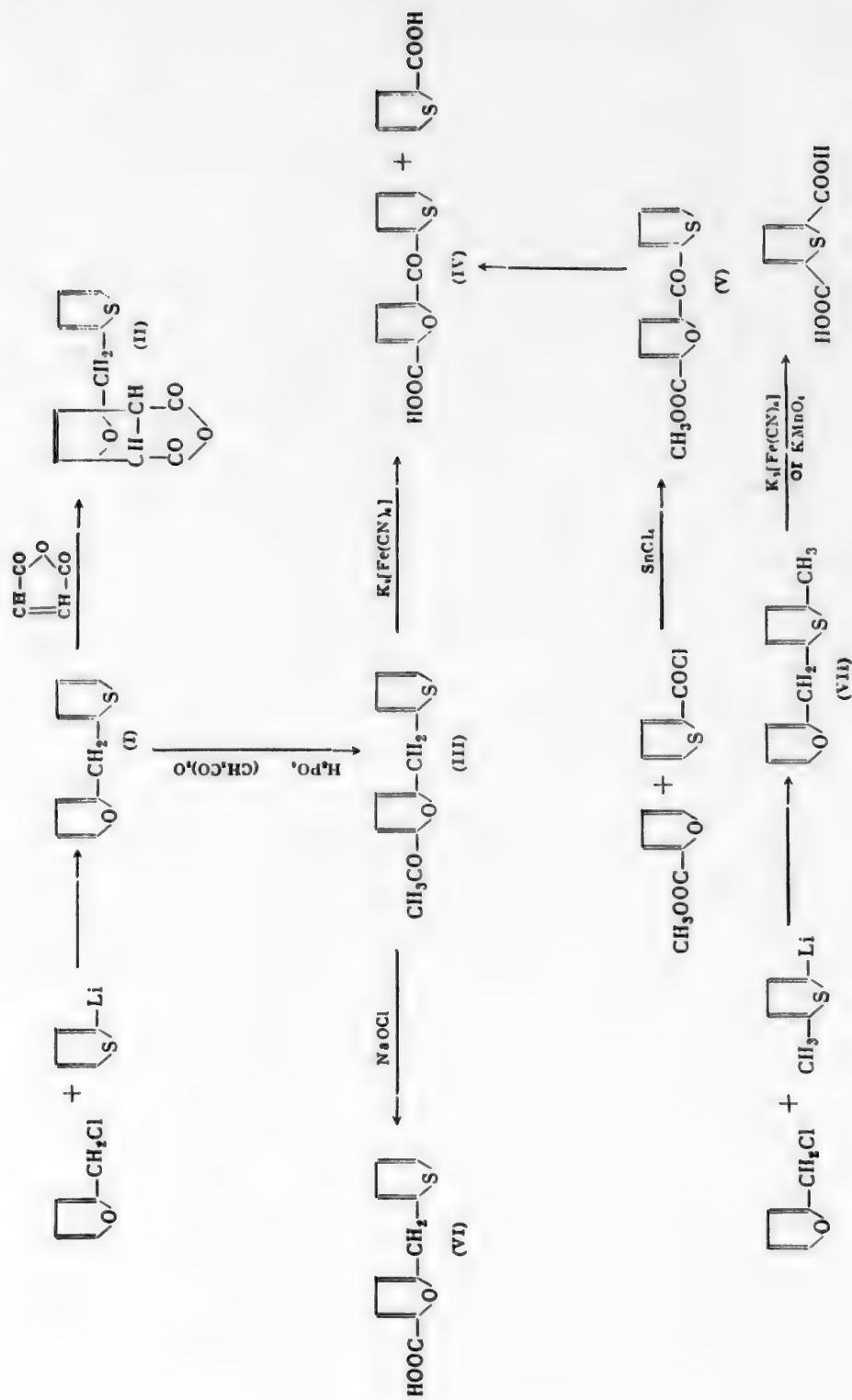
Found %: C 66.14, 65.93; H 5.03, 5.00; S 19.34, 19.10.  $C_9H_8OS$ . Calculated %: C 65.82; H 4.90; S 19.53.

The product was a colorless liquid soluble in common organic solvents, which darkened on standing.

2-Methyl-5-(2-furfuryl)thiophene (VII). This was prepared similarly from the 5-methyl-2-thienyllithium obtained from 29 g (0.296 mole) of 2-methylthiophene in 200 ml of absolute ether, 312 ml of a 1.045 N ethereal solution of butyllithium (0.326 mole), and 33.6 g (0.288 mole) of furfuryl chloride added without solvent during 15 min. Yield 18.7 g (36.5%, reckoned on furfuryl chloride).

B.p.  $85-88^{\circ}$  (3.5-4 mm),  $d_4^{20}$  1.1150,  $n_D^{20}$  1.5482,  $MR_D$  50.79; calc. 51.02.

Found %: C 67.29, 67.36; H 5.60, 5.60.  $C_{10}H_{10}OS$ . Calculated %: C 67.38; H 5.66.





3-(2-Thenyl)-3,6-endoxy-1,2,3,6-tetrahydrophthalic Anhydride (II). To a solution of 9.8 g (0.1 mole) of maleic anhydride in 12 ml of benzene at the temperature of incipient crystallization was added 16.4 g (0.1 mole) of 2-furyl-2-thienylmethane. The mixture evolved heat, turned yellow, and soon crystallized; the precipitate was washed with absolute ether. Yield 24.9 g (94.8%). M.p. 88.3-89° (from ethyl acetate, in a sealed capillary put into an apparatus heated to 85°).

Found %: C 59.30, 59.40; H 3.92, 3.91; S 12.04, 12.17.  $C_{13}H_{10}O_4S$ . Calculated %: C 59.13; H 3.84; S 12.23.

Acetylation of a Furan-Thiophene Mixture. To 10.2 g (0.15 mole) of furan, 12.6 g (0.15 mole) of thiophene, and 15.3 g (0.15 mole) of acetic anhydride at 0°, with stirring, 2.1 g of boron trifluoride etherate was added all at once, and the mixture was heated to 92°. After 15 min it was cooled to 2°, stirred for 45 min without cooling, and then diluted with 45 ml of water, neutralized with soda, and extracted with benzene. After removal of benzene and distillation in vacuo two fractions were isolated.

Fraction 1: B.p. 81-86° (27-28 min, 8.0 g- $n_D^{20}$  1.5092-2-acetylfuran containing 5.4% of 2-acetylthiophene (calculated on the basis of the sulfur content).

Found %: C 64.86, 65.01; H 5.57, 5.39; S 1.29, 1.49.  $C_6H_6O_2$ . Calculated %: C 65.44; H 5.49.  $C_6H_6OS$ . Calculated %: C 57.11; H 4.79; S 25.41.

Fraction 2: B.p. 98-101° (18 mm), 0.8 g- $n_D^{20}$  1.5408 (found %: S 14.81, 14.77)-a mixture of 41.8% of 2-acetylfuran and 58.2% of 2-acetylthiophene.

The total yield of 2-acetylfuran was 7.9 g (48%).

The benzene distillate, containing the bulk of the thiophene, was treated with 11.8 g (0.15 mole) of acetyl chloride in the presence of 43 g (0.165 mole) of stannic chloride. The benzene was distilled off, and two fractions were isolated from the residue.

Fraction 1: B.p. 78-90° (9 mm), 0.8 g- $n_D^{20}$  1.5398 (found %: S 14.58, 14.59)-a mixture of 57.4% of 2-acetylthiophene and 42.6% of 2-acetylfuran.

Fraction 2: B.p. 80-84° (9 mm), 10.8 g- $n_D^{20}$  1.5635-a mixture of 95.10% of 2-acetylthiophene and 4.9% of 2-acetylfuran.

Found %: C 57.94, 57.68; H 4.98, 4.92; S 24.22, 24.12.  $C_6H_6OS$ . Calculated %: C 57.11; H 4.79; S 25.41.  $C_6H_6O_2$ . Calculated %: C 65.44; H 5.49.

The total yield of 2-acetylthiophene was 10.8 g (57%).

Metalation of a Furan-Thiophene Mixture with Butyllithium. To a solution of 10.2 g (0.15 mole) of furan and 12.6 g (0.15 mole) of thiophene in 300 ml of absolute ether in an argon atmosphere, 135 ml (0.15 mole) of a 1.115N ethereal solution of butyllithium was added at (-3)-7° during 20 min, and after stirring for 2 hr without cooling, the solution was poured into a mixture of Dry Ice and 200 ml of absolute ether. The carbon dioxide was evaporated, 100 ml of water added, and the water layer acidified with dilute sulfuric acid; 15.4 g of a crystalline product was isolated, which was dissolved in ether and boiled with activated charcoal. After removing the ether there was obtained 14.8 g of a residue with m.p. 123-124°, containing 14.3 g (96.3%) of thiophene-2-carboxylic acid and 0.5 g (3.7%) of furan-2-carboxylic acid.

Found %: C 47.09, 47.20; H 3.10, 3.17; S 24.21, 23.97.  $C_6H_4O_2S$ . Calculated %: C 46.86; H 3.15; S 25.02.

The acid filtrate was treated with 10% aqueous sodium hydroxide solution, boiled down to half its original volume, acidified with sulfuric acid, and extracted with ether. After removing the ether there was obtained a crystalline product (4.5 g) containing 0.9 g (20%) of thiophene-2-carboxylic acid (found %: S 5.03, 5.00).

The total yield of thiophene-2-carboxylic acid was 15.2 g (79.2%).

Acetylation of 2-Furyl-2-thienylmethane. A mixture of 24.6 g (0.15 mole) of 2-furyl-2-thienylmethane, 23 g (0.225 mole) of acetic anhydride, and 1.8 g of 85% orthophosphoric acid was stirred for 1.5 hr at 65-70°, after which 100 ml of water was added at 5° and the mixture extracted with ether. The ethereal extract was washed with water, saturated sodium bicarbonate solution, and again water and then dried over magnesium sulfate, the ether driven off, and the residue distilled, 12.4 g (40%) of 5-(2-thenyl)-2-acetylfuran (III) being isolated. B.p. 147-150° (4 mm),  $d_4^{20}$  1.2059,  $n_D^{20}$  1.5862.

Found %: C 64.07, 63.87; H 5.13, 4.95; S 15.39, 15.35.  $C_{11}H_{10}O_2S$ . Calculated %: C 64.05; H 4.89; S 15.53.

Oxime: M.p. 109-110° (from aqueous alcohol).

Found %: N 6.32, 6.37.  $C_{11}H_{11}O_2NS$ . Calculated %: N 6.33.

Semicarbazone: M.p. 150-151.7° (from aqueous alcohol).

Found %: N 15.88, 15.71.  $C_{12}H_{13}O_2N_3S$ . Calculated %: N 15.96.

2,4-Dinitrophenylhydrazone: M.p. 152-153° (from an alcoholethyl acetate mixture).

Found %: N 14.65, 14.52.  $C_{17}H_{14}O_6N_4S$ . Calculated %: N 14.50.

Besides, there was obtained 4.5 g of a viscous, partly-crystallized liquid from which, on addition of ether, 1.2 g of the diacetyl derivative of 2-furyl-2-thienylmethane was isolated; m.p. 95.5-96.2° (from heptane).

Found %: C 62.96, 62.69; H 4.88, 4.90; S 12.74, 12.59.  $C_{13}H_{12}O_3S$ . Calculated %: C 62.88; H 4.87; S 12.91.

Oxidation of 5-(2-Thenyl)-2-acetylfuran (III) with Potassium Ferricyanide. A mixture of 5.4 g (0.026 mole) of 5-(2-thenyl)-2-acetylfuran, 134.5 g (0.41 mole) of potassium ferricyanide, 53.8 g (0.96 mole) of potassium hydroxide, and 800 ml of distilled water was stirred and boiled for 3 hr, after which the hot solution was filtered and boiled down to half its original volume. The potassium ferrocyanide which separated on cooling was filtered out and washed with a little ice water. The filtrate, combined with the wash water, was acidified with dilute (1:1) hydrochloric acid and extracted with ether. After removing the ether the solid residue (3.5 g) was dissolved in 150 ml of boiling distilled water. Precipitate "A" (1.2 g), consisting of 5-(2-thenyl)furan-2-carboxylic acid (IV), separated from solution on cooling. M.p. 199-201° (from water, n-nonane, and sublimation in vacuo); neutralization equivalent 220; calcd. 222.23.

Found %: C 53.74, 53.74; H 2.73, 2.54; S 14.05, 14.05.  $C_{10}H_6O_4S$ . Calculated %: C 54.05; H 2.72; S 14.43.

A mixed sample with keto acid (IV) prepared by condensation of thiophene-2-carbonyl chloride with methyl pyromucate and subsequent hydrolysis of the condensation product gave no depression on melting.

From an ethereal extract of the filtrate (from precipitate "A") was isolated precipitate "B" (1.4 g), m.p. 120.8-122.1° (after recrystallization from water and heptane and sublimation in vacuo), which was similar to thiophene-2-carboxylic acid in elementary composition, neutralization equivalent (found 126.7; calculated 128.15), and the character of absorption in ultraviolet ( $\lambda$  2460 Å,  $\epsilon$  9600 in alcohol; literature data [12]:  $\lambda$  2460 Å,  $\epsilon$  9100 in alcohol), but differed from it in melting point (literature data [13]: M.p. 128-129°).

Found %: C 47.41, 47.37; H 3.09, 3.23; S 24.77, 24.69.  $C_8H_6O_3S$ . Calculated %: C 46.86; H 3.15; S 25.02.

The somewhat lowered melting point and increased carbon content (0.5%) of thiophene-2-carboxylic acid were due to the difficulty of freeing the thiophene-2-carboxylic acid from the accompanying 5-(2-thenyl)-furan-2-carboxylic acid (IV).

Oxidation of 2-Methyl-5-(2-furfuryl)thiophene (VII) with Potassium Ferricyanide. A 4.0 g quantity (0.022 mole) of 2-methyl-5-(2-furfuryl)thiophene, 200 g (0.61 mole) of potassium ferricyanide, 80 g (1.43 mole) of potassium hydroxide, and 1200 ml of water were boiled for 8 hr with stirring. The solution was filtered while hot, cooled, extracted with ether, and the extract dried over calcium chloride. After solvent removal and distillation in vacuo 0.9 g of the original 2-methyl-5-(2-furfuryl)thiophene (VII) was isolated. The alkaline solution was treated as in the preceding. There was isolated 1.7 g of thiophene-2,5-dicarboxylic acid, which was converted to its dimethyl ester by means of 2.8 g of diazomethane in 600 ml of absolute ether. Yield 1.7 g (88%). M.p. 146.5-147° (from alcohol); (literature data [14]: M.p. 148.5-149.5°).

Found %: C 48.10, 47.99; H 4.08, 3.98; S 16.01, 15.86.  $C_8H_6O_4S$ . Calculated %: C 47.99, H 4.03; S 16.01.

Methyl 5-(Thenoyl)furan-2-carboxylate (V). To a solution of 6.3 g (0.05 mole) of methyl pyromucate and 7.3 g (0.05 mole) of thiophene-2-carbonyl chloride in 35 ml of anhydrous benzene was added a solution of 13 g (0.05 mole) of stannic chloride in 15 ml of dry benzene at 0-3° during 60 min; the mixture was stirred for 4 hr more at 28-29°. After 42 hr the mixture was poured into 100 g of crushed ice and the water layer extracted with benzene. The combined benzene solution was washed with water, saturated with soda solution, and again water, and the solvent was driven off. On distillation of the residue two fractions were isolated:

Fraction 1: B.p. 105-140° (50 mm), 5.1 g— $n_D^{20}$  1.5272, — apparently a mixture of thiophene-2-carbonyl chloride and methyl pyromucate.

Fraction 2: B.p. 190-195° (6 mm), 2.2 g—a viscous, instantly crystallizing liquid consisting of ester (V). Yield 18.9%, m.p. 113-114.2° (from alcohol).

Found %: C 56.08, 55.85; H 3.54, 3.39, S 13.45, 13.49.  $C_{11}H_6O_4S$ . Calculated %: C 55.92; H 3.41; S 13.57.

5-(2-Thenoyl)furan-2-carboxylic Acid (IV). A mixture of 2.4 g (0.01 mole) of methyl 5-(2-thenoyl)furan-2-carboxylate, 1.7 g (0.03 mole) of potassium hydroxide, and 15 g of alcohol was boiled for 4 hr in a water bath. The alcohol was distilled off in vacuo, the solid residue dissolved in 20 ml of water, and the solution washed with benzene and ether and acidified with 50% sulfuric acid. Yield 1.2 g (54%), m.p. 200-201.5° (from water, n-nonane, and sublimation in vacuo).

Found %: C 53.86, 53.72; H 2.74, 2.68; S 14.00, 14.09.  $C_{10}H_6O_4S$ . Calculated %: C 54.05; H 2.72; S 14.43.

5-(2-Thenyl)furan-2-carboxylic Acid (VI). Into a mixture of 6.6 g (0.165 mole) of sodium hydroxide, 9 ml of water, and 37.5 g of ice was passed 4.8 g (0.0675 mole) of chlorine during 2-3 min, after which 3.1 g (0.015 mole) of 5-(2-thenyl)-2-acetylfuran (III) was added at 65-70° to the hypochlorite solution obtained. The mixture was stirred for 50 min at 65-70° and gradually cooled to 25-30°, after which 6 ml of concentrated sodium bisulfite solution was added. After 20 min the cooled mixture was acidified with concentrated hydrochloric acid and the resulting precipitate washed with ice water and dried. Yield 2.4 g (76.5%). M.p. 120-121° (from heptane and sublimation in vacuo). Neutralization equivalent 208; calcd. 208.24.

Found %: C 57.60, 57.58, H 3.91, 4.14; S 15.37, 15.29.  $C_{10}H_6O_4S$ . Calculated %: C 57.68; H 3.87, S 15.40.

#### SUMMARY

1. 2-Furyl-2-thienylmethane was synthesized in 45-53% yield by treating 2-thienyllithium with furfuryl chloride. 2-Methyl-5-(2-furfuryl)-thiophene was prepared similarly from 5-methyl-2-thienyllithium and furfuryl chloride.
2. On acetylation of 2-furyl-2-thienylmethane with acetic anhydride in the presence of orthophosphoric acid the acetyl group enters the furan ring in the  $\alpha$ -position; in this case 5-(2-thenyl)-2-acetylfuran is formed in 40-46% yield, along with a little of the diacetyl derivative.
3. Oxidation of 5-(2-thenyl)-2-acetylfuran with potassium ferricyanide in an alkaline medium gives 5-(2-thenoyl)furan-2-carboxylic acid and thiophene-2-carboxylic acid, whereas its oxidation with sodium hypochlorite gives 5-(2-thenyl)furan-2-carboxylic acid.
4. The reaction of thiophene-2-carbonyl chloride with methyl pyromucate in the presence of stannic chloride gives methyl 5-(2-thenoyl)furan-2-carboxylate, which was converted by hydrolysis to 5-(2-thenoyl)furan-2-carboxylic acid.

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# SYNTHESIS OF CERTAIN ORGANOMETALLIC COMPOUNDS BY MEANS OF TRIALKYLALUMINUMS

L. I. Zakharkin and O. Yu. Okhlobystin

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Trialkylaluminums are widely used for the synthesis of various heteroorganic compounds [1, 2]. The comparative mildness of the alkylating action of trialkylaluminums and the possibility of widely varying the experimental conditions, make it possible to obtain by their means not only fully alkylated derivatives, but also incomplete-alkylation product, which in some cases is of interest in itself [3].

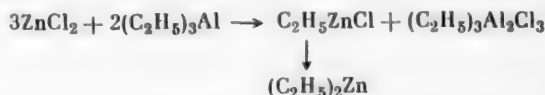
In a continued investigation of the alkylating ability of trialkylaluminums in the synthesis of heteroorganic compounds we studied the interaction of triethyl- and triisobutylaluminum with zinc, boron, gallium, germanium, and stannic chlorides.

The literature data on the interrelations of alkylaluminums and -zincs are contradictory at first glance. On the one hand, the preparation of triethylaluminum by the reaction of sesquiethylaluminum sesquiodide with diethylzinc is described [4]; on the other, the preparation of dialkylzincs from zinc halides and sesquialkylaluminum sesquihalides [5] or trialkylaluminums [6] is proposed in later works. However, since aluminum and zinc have nearly the same electronegativity, both the direct and reverse reactions are possible in principle.

Therefore we studied the interrelations of alkyl and halogen compounds of zinc and aluminum in greater detail. In this case it was found that diethylzinc reacts with aluminum chloride, and triethylaluminum reacts with zinc chloride. Therefore exchange reactions between organoaluminum and -zinc compounds are reversible to a considerable degree and may be used for the preparation of both types of organometallic compounds. The interaction of equimolar quantities of diethylzinc and aluminum chloride gave a mixture of ethylaluminum dichloride and diethylaluminum chloride whose composition was very close to that of sesquiethylaluminum sesquichloride.



On the other hand, zinc chloride is alkylated by triethylaluminum.

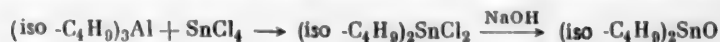


It is characteristic that diethylaluminum chloride still alkylates zinc chloride, whereas ethylaluminum dichloride at 100° and without solvent does not give diethylzinc on treatment of the reaction mixture.

The reaction of gallium chloride with trimethylaluminum has the same equilibrium character; with some excess of trimethylaluminum, trimethylgallium is formed in a yield exceeding 64%.

The alkylation of germanium tetrachloride goes a little more readily than in the case of stannic chloride [1]: tetraethyl- and tetraisobutylgermanium are obtained in 73% yield.

The formation of tri- and especially tetraalkyl derivatives of tin on interaction of stannic chloride with trialkylaluminums is well known [1, 7]. Under certain conditions, however, the reaction of stannic chloride with triisobutylaluminum leads to dichlorodiisobutyltin as the main product; this is easily isolated from the reaction mixture in the form of the oxide.



This reaction may be of interest in the synthesis of dialkyltin derivatives, which have found a number of important applications in recent years.

It was found that the interaction of trialkylaluminums with excess boron trichloride at 0° and without solvent may be a convenient method of alkylchloroborane synthesis.



At a higher temperature the reaction apparently can be used also to prepare dialkylchloroboranes. Obviously the reaction does not go through the stage of trialkylborane formation with further reaction of the latter with excess boron trichloride, since this last reaction takes place only on heating to 100°.

#### EXPERIMENTAL PART

Reaction of Zinc Chloride with Triethylaluminum. To 41 g of anhydrous zinc chloride, ground to a powder, was carefully added 22.8 g of triethylaluminum with stirring and in an argon atmosphere. Much heat was evolved in the reaction. The mixture was heated for 3 hr at 100°, after which the diethylzinc was distilled off in vacuo into a cooled trap. Yield 6.6 g; b.p. 118°,  $n_D^{20}$  1.182.

Reaction of Aluminum Chloride with Diethylzinc. Similarly 7.2 g of aluminum chloride and 6.75 g of diethylzinc on fractionation in vacuo gave 6.0 g of a mixture of ethylaluminum dichloride and diethylaluminum chloride, b.p. 43-49° (1 mm), and traces of diethylzinc (in the trap).

Found %: C 27.22, 27.29; H 6.02, 6.02; Al 21.92, 21.93; Cl 44.42, 44.34.  $(\text{C}_2\text{H}_5)_2\text{Al}_2\text{Cl}_2$ . Calculated %: C 29.11; H 6.1; Al 21.79; Cl 42.97.

Reaction of Diethylaluminum Chloride with Zinc Chloride. Twelve g of diethylaluminum chloride and 13.6 g of zinc chloride (100°, 3 hr) gave 2.0 g of diethylzinc, b.p. 117-118°.

Under the same conditions no diethylzinc at all was obtained from 20.0 g of zinc chloride and 20.5 g of ethylaluminum dichloride (even on heating to 150°).

Trimethylgallium. To 17.6 g of freshly-distilled gallium trichloride was added 14 g of trimethylaluminum (with stirring and in an argon atmosphere). Heat was evolved in the reaction; after all the trimethylaluminum had been added, the mixture was heated for 2 hr at 80°. Trimethylgallium (b.p. 56-60°) (literature data [8]: B.p. 55.7°) and dimethylaluminum chloride (b.p. 114-121°) were distilled from the reaction mixture. Eight ml of trimethylaluminum was added to the residue in the flask, after which trimethylgallium again was distilled off. Yield 7.4 g (64.5%).

Tetraethylgermanium. To 18.0 g of triethylaluminum, 25.6 g of germanium tetrachloride, freshly-distilled over mercury, was added with stirring and in a nitrogen atmosphere, at such a rate that the mixture temperature was maintained between 80 and 90°. When the temperature was decreased, the reaction went intermittently. After this the mixture was heated for 6 hr at 120-130°, then diluted with ether and decomposed with an excess of 20% sodium hydroxide. The ether layer was washed with dilute acetic acid, dried with calcium chloride, and distilled. Yield 15.9 g (72.9%).

B.p. 162-163°;  $n_D^{20}$  1.4485,  $d_4^{20}$  0.9942. Literature data [9]: B.p. 163.5°,  $n_D^{20}$  1.4430,  $d_4^{20}$  0.9932.

Tetraisobutylgermanium. Similarly 26.5 g of germanium tetrachloride and 37 g of triisobutylaluminum gave 24.0 g (73.1%).

B.p. 159-160° (50 mm),  $n_D^{20}$  1.4580,  $d_4^{20}$  0.9364.

Found %: C 63.32, 23.20; H 12.08, 12.04; Ge 24.05, 24.20.  $(\text{C}_4\text{H}_9)_4\text{Ge}$ . Calculated %: C 63.83; H 12.05, Ge 24.11.

Isobutyldichloroborane. a) To 54 g of boron trichloride, 19 g of triisobutylaluminum was added in a current of pure nitrogen, the mixture being stirred and ice-cooled at such a rate that the reaction-mixture temperature did not rise above 2° (about 1.5 hr). The cooling was stopped, the mixture gradually heated to room temperature, and the excess boron trichloride distilled off. The residue was distilled in vacuo (8 mm) into a cooled trap. On distillation in a column (10 t. p.) 30.2 g (57.5%) of isobutyldichloroborane and 5.5 g of a high-boiling fraction were obtained.



B.p. 96.2° (735 mm). Literature data [10]: B.p. 96.8° (754 mm)<sup>2</sup>.

Found %: C 34.83, 34.95; H 6.72, 6.71; B 8.13, 7.90.  $C_4H_9Cl_2B$ . Calculated %: C 34.60; H 6.53; B 7.79.

b) In a similar experiment 120 g of boron trichloride and 40 g of triisobutylaluminum at the boiling point of boron trichloride gave 24 g of isobutyldichloroborane and 20.5 g of diisobutylchloroborane.

B.p. 155-156° (745 mm),  $n_D^{20}$  1.4158. Literature data [11]: B.p. 156° (747 mm),  $n_D^{20}$  1.4160.

Ethyldichloroborane. An 86.5 g quantity of boron trichloride and 14 g of triethylaluminum at a temperature of (-6)-(-5°) gave 23.5 g (50%).

B.p. 50.8° (744 mm). Literature data [10]: B.p. 50.8° (745 mm).

Diisobutyltin Oxide. To 78.2 g of anhydrous stannic chloride in a nitrogen atmosphere, with stirring, 42 g of triisobutylaluminum was added at such a rate that the temperature was maintained between 85 and 90°. The mixture was stirred and heated to 110-115° for 2 hr and then decomposed by pouring into sodium hydroxide solution. The precipitated infusible powder was washed with water, alcohol, and ether and dried at 100°. It could be purified by reprecipitation from hydrochloric acid solution with aqueous-alcoholic ammonia. Yield 51.3 g (70%).

Found %: Sn 47.65, 47.52.  $C_8H_{18}OSn$ . Calculated %: Sn 47.58.

#### SUMMARY

1. It was shown that alkyl-halogen exchange reactions in a number of zinc and aluminum compounds are reversible.
2. On treatment of gallium and germanium chlorides with trialkylaluminums, the full alkyl derivatives of these elements are formed.
3. The interaction of trialkylaluminums with boron and stannic chlorides may be used to prepare alkyldichloroboranes and dialkyltin compounds.

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## INVESTIGATIONS IN THE ANTHRAQUINONE SERIES

### XXXIV. PECULIARITIES OF THE CHLORINATION OF ANTHRAQUINONE- $\beta$ -SULFONIC ACID TO $\beta$ -CHLOROANTHRAQUINONE\*

V. V. Kozlov and A. A. Davydov

G. V. Plekhanov Moscow Institute of the National Economy

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It is well known that in industrial production  $\beta$ -chloroanthraquinone is prepared by the Friedel-Crafts reaction from phthalic anhydride and chlorobenzene [1]. The following methods of preparing  $\beta$ -chloroanthraquinone are of theoretical interest: Treatment of a 2-anthraquinonediazonium salt with chlorine in hydrochloric acid [2]; oxidation of 2,9,10-trichloroanthracene [3]; chlorination with replacement of the sulfo group by chlorine on treatment of anthraquinone- $\beta$ -sulfonic acid with chlorate in hydrochloric acid [4], or by active chlorine formed by the action of light on a solution of anthraquinone- $\beta$ -sulfonic acid in hydrochloric acid [6]; oxidative chlorination of anthracene-2-sulfonic acid [7]. The main difficulty, preventing the wide use of oxidative chlorination both for  $\beta$ -chloroanthraquinone synthesis and the quantitative analysis [8] of anthraquinone- $\beta$ -sulfonic acid, is the long duration of the process and the nonquantitative yields. The rate constants of replacement of sulfo groups by chlorine for anthraquinone- $\beta$ -sulfonic acid [9] at various temperatures are 0.4-0.5 times those for the  $\alpha$ -sulfonic acid. It is said [10] that the  $\beta$ -sulfo group in anthraquinonesulfonic acids is replaced 20 times as easily by chlorine as the  $\alpha$ -sulfo group, and [11] that the preparation of  $\beta$ -chloroanthraquinone in a yield, equal to that of  $\alpha$ -chloroanthraquinone, requires twice as much time, chlorate, and hydrochloric acid. Chlorination of anthraquinone- $\beta$ -sulfonates with gaseous chlorine in the presence of ammonium chloride [12] for 1 hr leads to  $\beta$ -chloroanthraquinone in 31.1% yield. Lower mobility of the  $\beta$ -sulfo group attached to anthraquinone, in comparison with the  $\alpha$ -group, is observed also in the case of other conversions of anthraquinone- $\beta$ -sulfonic acids.

In a study of the importance of various factors in the oxidative chlorination of  $\alpha$ -sulfonic acid [4] we extended these observations to the  $\beta$ -sulfonic acid. In Fig. 1 it is evident that the maximum effect of anthraquinone- $\beta$ -sulfonic acid chlorination by chlorate depends on the optimum hydrochloric acid concentration. The rate of the anthraquinonesulfonic acid chlorination process may be considerably increased by using mixtures of hydrochloric acid with such acids as sulfuric, nitric, and phosphoric (Fig. 2), the rate of chlorination of the  $\beta$ -isomer being 0.33-0.4 times that of the  $\alpha$ -isomer. It is expedient to chlorinate anthraquinone- $\beta$ -sulfonic acid at a slightly higher temperature (102-104°) not only with chlorate, but also when other oxidizing agents, able to form active chlorine with hydrochloric acid, are used. Contrary to anthraquinone- $\alpha$ -sulfonic acid [14], however, replacement of the sulfo group in the  $\beta$ -isomer takes place with great difficulty under these conditions. The most convenient oxidizing agent that can produce a steady concentration of active chlorine is a chlorate in a mixture of hydrochloric and sulfuric acids which provides the optimum acidity of the medium, required for increased polarization of the sulfo group in the anthraquinonesulfonic acid.

#### EXPERIMENTAL PART

Pure sodium anthraquinone- $\beta$ -sulfonate (with benzylisothiocarbamide-tablets from water [13], m.p. 211-212° under the microscope) was used for the chlorination. In the chlorination experiments all reaction components were mixed beforehand, at the beginning of the process, in the form of solutions heated to boiling, in a three-neck flask provided with a stirrer, condenser, and hydraulic seal. The  $\beta$ -isomer could be chlorinated by chlorate only when the HCl concentration was at least 0.26-0.3 N. The optimum HCl concentration for the  $\beta$ -isomer was 0.9-1.0 N. Hydro-

\* For article XXXIII see ZHOKh, 31, 3448 (1961).

chloric-sulfuric acid mixtures had the best positive effect. Chlorination of 0.004 mole of anthraquinone- $\beta$ -sulfonic acid in a mixture of 0.026 mole of HCl (0.13 N) and 1.2 moles of phosphoric acid for 1 hr gave  $\beta$ -chloroanthraquinone in 66% yield. A quantitative yield of  $\beta$ -chloroanthraquinone could be obtained by chlorinating for 3 hr in a mixture of 0.1 mole of HCl and 0.24 mole of  $H_2SO_4$ . A quantitative yield could be obtained within 2 hr in a hydrochloric-sulfuric acid medium by using not 1.8, but 2.5-3.0 moles of chlorate per mole of sodium anthraquinone- $\beta$ -sulfonate.

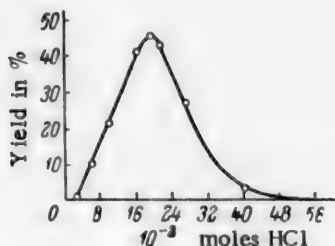


Fig. 1. Yield of  $\beta$ -chloroanthraquinone with respect to the hydrochloric acid concentration in a hydrochloric-sulfuric acid medium.

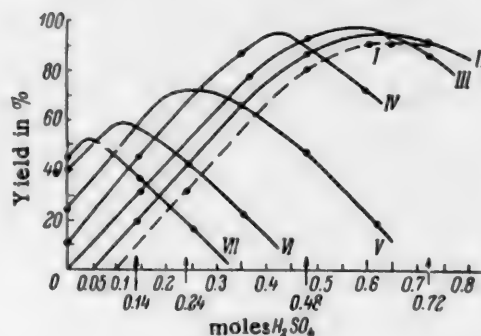


Fig. 2. Chlorination of anthraquinone- $\beta$ -sulfonic acid by chlorate with respect to the optimum hydrochloric acid concentration in a hydrochloric-sulfuric acid medium. I) 0.010; II) 0.016; III) 0.026; IV) 0.52; V) 0.105; VI) 0.157; VII) 0.180 mole of HCl.

When potassium bichromate was used in hydrochloric-sulfuric acid mixtures of various compositions, mainly with high hydrochloric acid concentrations, the maximum yield of  $\beta$ -chloroanthraquinone, obtained in 1 hr, was 38%. Chlorination of anthraquinone- $\beta$ -sulfonic acid with permanganate as the oxidizing agent was possible at a much lower hydrochloric acid concentration than when chlorate or especially bichromate was used. However, the reaction was also slow, and yields of  $\beta$ -chloroanthraquinone did not exceed 15% in 1 hr, although the yield could be raised to 49% by using hydrochloric-sulfuric acid mixtures. Despite the relatively low mobility of the  $\beta$ -sulfo group, its replacement by chlorine in a hydrochloric-sulfuric acid mixture by means of various oxidizing agents began at 80° or less, whereas  $\beta$ -chloroanthraquinone was not formed in hydrochloric acid alone under these conditions. Nevertheless, in the case of permanganate the process was not noticeably accelerated by a considerable temperature rise of the medium. Anthraquinone- $\beta$ -sulfonic acid could be chlorinated also by means of manganese dioxide. When 2 g of pyrolusite was used with 1.23 g of sodium anthraquinone- $\beta$ -sulfonate in a hydrochloric-sulfuric acid mixture (0.015-0.026 mole of HCl and 0.98 mole of  $H_2SO_4$ ),  $\beta$ -chloroanthraquinone was obtained in yields up to 60% in 3 hr at 108-110°. Still greater yields were obtained by using active manganese dioxide and then a mixture of sodium chloride and sulfuric acid.

#### SUMMARY

1. The conditions of replacement of the sulfo group by chlorine in the oxidative chlorination of anthraquinone- $\beta$ -sulfonic acid were studied. Conversion of the latter proceeds 0.33-0.4 times as rapidly as that of the  $\alpha$ -isomer. The most favorable conditions are brought about by using hydrochloric-sulfuric acid mixtures containing 2-3 times as much sulfuric acid as those used in chlorinating the  $\alpha$ -isomer.

2. The possibility of replacing the sulfo group in anthraquinone- $\beta$ -sulfonic acid by oxidative chlorination using oxidizing agents other than chlorates was shown.

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# ROLE OF COMPLEX-FORMING ADDITIVES IN THE SYNTHESIS OF PHTHALOCYANINES

## II. INFLUENCE OF COMPOUNDS OF PHOSPHORIC ACID, CHROMIUM OXIDE, AND TUNGSTEN TRIOXIDES ON THE FORMATION OF Fe PHTHALOCYANINES

A. P. Rudenko and N. P. Dobrosel'skaya

The M. V. Lomonosov Moscow State University

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Original article submitted December 2, 1960

As we have shown [1], the formation of Fe phthalocyanines from phthalamide and iron powder is considerably accelerated by small additions of heteropoly compounds, while, conversely, large additions of phosphoric acid, ammonium phosphate, ammonium molybdate, etc., inhibit it. The action of these additives, which have an acid character, is due to the formation of intermediate chemical compounds with the reactants which possess basic properties. It was of interest to continue the investigation of the influence of the concentration of complex-forming additives on the formation of Fe phthalocyanines using derivatives of phosphoric acid, chromium, and tungsten as examples, and to compare the results and the material obtained earlier [1] with data relative to the stability of additives in the form of acids and ammonium salts, since results already obtained indicate the presence of a connection between the dependence of the reaction of the additives on their concentrations and the stability of the compounds formed by them.

In the present work, the oxides of tungsten, molybdenum, and chromium, or the corresponding acids and heteropoly acids, which are stable under the experimental conditions, have been investigated as complex-forming additives. The formation of Fe phthalocyanines takes place at a considerable velocity even without the addition of the additives mentioned (see [1] and Figs. 1 and 2). Therefore, the effect of the action of the additives induced reduced to only some change in the rate of the reaction, leading to a change in the yield of product after the same intermediate time.

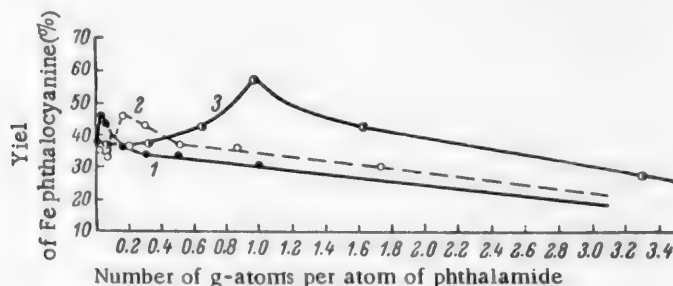


Fig. 1. Influence of the concentration of added oxides on the yield of Fe phthalocyanines. 1)  $\text{WO}_3 \cdot \text{H}_2\text{O}$ ; 2)  $\text{MoO}_3$ ; 3)  $\text{Cr}_2\text{O}_3$ .

In the region of high concentrations of additive, a relatively lower catalytic activity is observed for tungsten trioxide and a relatively higher activity for chromium oxide than for molybdenum trioxide. This phenomenon occurs in concentrations of additives higher than 0.5 g-atoms of the corresponding metal per one mole of initial phthalamide. The relative catalytic activity of ammonium phosphomolybdate proved to be higher than that of ammonium phosphotungstate at all appreciable concentrations of the additives. However, in the region of low concentrations, the ratio

of the relative catalytic activities changes, so that tungsten trioxide is most active at a concentration of about 0.10 g-atoms of tungsten per mole of phthalamide. However, at a concentration of 0.10-0.45 g-atoms of molybdenum, molybdenum trioxide becomes the most active.

Thus, the same effect of the action of additives according to the concentration is observed here, which agrees with the results obtained earlier [1]. A definite region of concentrations exists (see Figs. 1 and 2, and the table) in which the activating action of the additives on the formation of Fe phthalocyanine is shown. On raising the concentration above this limit, passivation of the process sets in, the more the higher the concentration of the additive. In addition, for each of the additives, a definite concentration exists at which its activating action is a maximum.

Activating and Passivation Action of Additives on the Formation of Fe Phthalocyanine as a Function of the Concentration

Additive	Maximum activating action of the additive (in % of the yield of Fe phthalocyanine without a catalyst)	Concentration of additive (in g-atom per 1 mole of phthalamide)			
		At the point of maximum activity	At the limits of the activating action	At 50% suppression of the synthesis of Fe phthalocyanine	At complete cessation of the process
$(\text{NH}_4)_2\text{H}_2\text{P}_2\text{O}_7$	0	0	0	0.2	0.7
$\text{H}_3\text{PO}_4$	0	0	0	0.4	1.0
$(\text{NH}_4)_3\text{PO}_4 \cdot 12\text{WO}_3 \times 6\text{H}_2\text{O}$	0	—	0.12		
$(\text{NH}_4)_3\text{PO}_4 \cdot 12\text{MoO}_3 \times 6\text{H}_2\text{O}$	42	0.1	0.20	2.2	
$\text{WO}_3 \cdot x\text{H}_2\text{O}$	24	0.02	0.20	3.5	
$\text{MoO}_3$	24	0.2	0.8	4.0	
$\text{Cr}_2\text{O}_3$	50	1.0	2.3	4.5	

The compounds studied can be arranged in the following order with respect to the increase in the magnitude of the limiting concentrations at which the transition from activating to passivating action is observed: ammonium phosphotungstate, ammonium phosphomolybdate, tungsten trioxide, molybdenum trioxide, chromium oxide. These compounds fall into the same sequence with respect to the concentration of additive at which a 50% reduction in the yield of Fe phthalocyanine in comparison with that obtained without a catalyst is reached. It is interesting to note that the additives monoammonium phosphate and orthophosphoric acid, which exhibit only a passivating action at any concentration, may, completely logically, occupy the first place in the given sequence. Thus, in the case of monoammonium phosphate and phosphoric acid, the region of activating action of the additive is practically zero; the phenomenon of marked passivation which leads to the complete cessation of the process on the addition of 1 g-atom of phosphorus per 1 mole of phthalamide [1] appears immediately. In the case of ammonium phosphotungstate, the addition of less than 0.12 g-atoms of tungsten is accompanied neither by activation nor by passivation of the process, but a further increase in the concentrations leads to passivation. For ammonium phosphomolybdate, clearly expressed activation of the process takes place in the region of concentrations up to 0.2 g-atoms of molybdenum, and passivation occurs at a higher concentration. For the following members of the series, a gradual widening of the field of activation

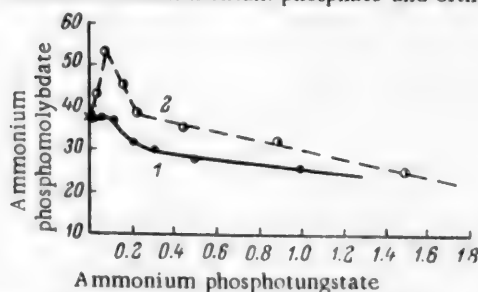


Fig. 2. Influence of the concentration of added heteropoly acids on the yield of Fe phthalocyanine. 1) Ammonium phosphotungstate; 2) ammonium phosphomolybdate.

of the series, a gradual widening of the field of activation



is observed. In all cases, an increase in the concentration of additive above the limiting activating value leads to a progressive inhibition of the process, the rate of inhibition decreasing in the sequence discussed.

If the thermal stability of phosphoric, tungstic, molybdic, and chromic acids, and their heteropoly acids and ammonium salts is considered on the basis of information in the literature [2] they may be placed in the following order of decreasing stability: Phosphorus compounds, tungsten compounds, molybdenum compounds, chromium compounds. The sequence found above according to increasing ranges of concentration of the additives exhibiting activating action and according to a decrease of their passivating action correlates well with the sequence of diminishing thermal stability of the acids and the ammonium salts corresponding to the additives taken. Here, if the additives taken are not themselves the acids considered or their ammonium salts, the correlation mentioned may be regarded as the capability of the additives of being converted into these compounds or of being obtained from them under the experimental conditions. The fact that chromium oxide, which corresponds in this sense to chromic acid and its ammonium salt, does not depart from the sequence found with respect to its catalytic activity, in spite of valency of the chromium from 6 to 3, deserves attention.

The reason for the observed correlation between the increase in activating action of the additives on the formation of Fe phthalocyanine and the decrease of the thermal stability of the additives taken in the form of acids and their ammonium salts apparently consists in the fact that intermediate chemical compounds of the additive-catalysts with the reactants, which play a decisive role in the process, possess different stabilities. The formation of these intermediate compounds ("ammonium-like" compounds) takes place as a result of the acidic character of the additives and the basic properties of the amide groups of phthalamide and the products of its condensation. The relative stability of the ammonium-like compounds may be evaluated, probably, from the stability of the ammonium compounds analogous to them, which in its turn is similar to the stability of the acids themselves, as follows from an analysis of the appropriate literature data [2].

The intermediate ammonium-like compounds and complexes, being mainly surface chemical compounds at the surface of the solid additive-catalysts, have not been isolated individually. However, the kinetic data obtained confirm the reality of their existence quite satisfactorily. The experimental data also indicate the breadth of the limits of change of the stability of these intermediate compounds according to the nature of the initial additives—from the stability of the actual chemical compounds of phthalamide with phosphoric acid to the stability of the adsorption complex of phthalamide with chromium oxide. The nature of these formations as intermediate forms of the interaction of the reactants and the additives is the same in all cases studied, which is confirmed by the existence of the observed gradation of the transition from the most stable intermediate compounds of the salt-like type to the least stable intermediate complexes of the adsorption type.

## EXPERIMENTAL PART

**Experimental procedure.** The experiments were carried out under static conditions in a melt of phthalamide at 240°, at atmospheric pressure, and with the continual stirring of the reaction mass [1]. The time of an experiment was 2 hours. In each experiment, 0.04 g-mole of phthalamide, 0.01 g-atom of powdered iron, and 0.12 g-mole of urea, added gradually during the course of the experiment, and a definite amount of catalyst (from 0 to 3 g-atoms of the appropriate element per 1 mole of phthalamide) were used. All the experiments with different concentrations of any one additive were carried out simultaneously. At the end of the experiments, the solidified melt was subjected to appropriate working up [1] for isolating the Fe phthalocyanine in pure form. In the case of experiments with chromium oxide, a mixture of Fe phthalocyanine and the additive introduced during the experiment was isolated and this was taken into account. The yields of Fe phthalocyanine were calculated on the phthalamide used. The compounds employed in the investigation were used in the form of commercial preparations of "chemically pure" and "pure for analysis" grades. The initial phthalamide was synthesized in accordance with the data of reference [1].

## SUMMARY

1. The influence of the concentration of certain additives on the formation of Fe phthalocyanine from phthalamide and iron under static conditions at 240° has been investigated. It has been confirmed that small concentrations activate the process and large concentrations passivate it, the additives investigated being arranged in the following series with respect to the breadth of the region of activating concentrations and to lessening of passivating action: Phosphoric acid, ammonium phosphotungstate, ammonium phosphomolybdate, tungsten trioxide, molybdenum trioxide, chromium oxide.

2. The effect of the action of the additives studied on the formation of Fe phthalocyanine (activation, passivation, and their degree) is determined by the stability of the intermediate compounds and complexes of the reactants and the reaction products with the additives introduced and the concentrations of the latter.

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# INVESTIGATION IN THE FIELD OF ALKANE SULFONIC ACIDS

## XXV. HALOGENATED ALKANESULFON-p-PHENETIDIDES

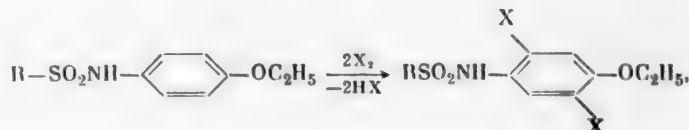
A. G. Kostova

Voronezh State University

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pp. 3671-3675, November, 1961

Original article submitted November 16, 1960

As a development of our previous investigation, [1], the present work was devoted to a study of the chlorination and bromination of p-phenetidides of methane-, ethane-, propane-, and butanesulfonic acids. It was established that the two reactions proceed in a similar manner to the chlorination and bromination of the p-anisidides, i.e., the main reaction products are 2,5-dichloro- or dibromo-p-phenetidides; in the case of chlorination, a small amount of tetrachlorobenzoquinone is formed as a by-product; in bromination no similar product was isolated.



where X = Cl or Br.

It was noted that with a rise in the temperature and an increase in the time of chlorination and the amount of solvent the yields of dichlorophenetidides diminished. The main mass of dichloro-p-phenetidides separated out during the reaction, but a small fraction was obtained in admixture with tetrachlorobenzoquinone only after evaporating the solvent; the tetrachlorobenzoquinone was washed out partially with alcohol, from which it crystallized on cooling. The residue of dichlorophenetidide contaminated with tetrachlorobenzoquinone was purified by adsorption chromatography. Alumina was used as the adsorbent and acetone as the solvent. The structure of the dihalogeno derivatives of the p-phenetidides was determined, as in the previous cases, by hydrolysis to the corresponding amines.

It is known that many phenetidides of alkane sulfonic acids possess antipyretic, sedative, and lenitive properties [2]. There is every reason to assume that their halogen derivatives will possess similar properties. The compounds obtained are of interest from this point of view.

## EXPERIMENTAL PART

Chlorination of alkanesulfon-p-phenetidides (Table 1). The p-phenetidide was dissolved in dichloroethane and chlorine was passed into the cooled solution at the rate of 198 ml per minute. The clear mixture became turbid, and the precipitate of dichlorophenetidide which separated was removed, washed with dichloroethane, dried, and recrystallized from hot alcohol. The dichloroethane filtrate was evaporated leaving a viscous reddish-orange oil and a deposit. The residue was treated with alcohol, the oil dissolving it and the deposit was separated and dried. The alcoholic filtrate was boiled and cooled slowly. Fine golden yellow crystals of tetrachlorobenzoquinone (chloranil) separated, with m.p. 290°. On mixing alcoholic solutions of aniline and chloranil, characteristic silver-brown crystals of the dianiline derivative separated [3].

Found %: N 9.64.  $\text{C}_{18}\text{H}_{12}\text{O}_2\text{N}_2\text{Cl}_2$ . Calculated %: N 9.72.

The deposit, consisting of a mixture of dichlorophenetidide and tetrachlorobenzoquinone was separated by adsorption chromatography. Chromatographic alumina was used as the adsorbent, being previously moistened in the adsorption column with petroleum ether, and acetone was used as the solvent. A solution of 0.4 g of the mixture of the

TABLE 1

Serial No.	Formula of the compound	p-Phen- eride (in g)	Taken initially (in ml)	Time of chlorination (in min)	Reaction temperature (in min)	Yield		M.p.	% N		% Cl		% S	
						Dichloro- phenetide (in g)	Tetrachloro- benzoquinone (in g) (in %)		found	calc.	found	calc.	found	calc.
1	$\begin{array}{c} \text{CH}_3\text{SO}_2\text{NH}-\text{C}_6\text{H}_4-\text{Cl} \\ \text{C}_{11}\text{H}_{17}\text{O}_2\text{NSCl}_2 \end{array}$	2.0	60	30	19-10°	0.71	traces	170-171°	6.48	6.51	33.11	33.08	14.90	14.88
		2.0	20	25	17-9	0.60	0.05							
		2.0	15	15	13-7	0.55	0.05							
2	$\begin{array}{c} \text{C}_6\text{H}_5\text{SO}_2\text{NH}-\text{C}_6\text{H}_4-\text{Cl} \\ \text{C}_{10}\text{H}_{13}\text{O}_2\text{NSCl}_2 \end{array}$	2.0	15	40	40-30	0.97	0.155	133-134	6.08	6.11	30.28	30.56	13.91	13.97
		2.0	15	40	7-5	0.96	0.1							
		2.0	15	15	29-19	0.98	0.04							
3	$\begin{array}{c} \text{CH}_3\text{SO}_2\text{NH}-\text{C}_6\text{H}_4-\text{Cl} \\ \text{C}_{10}\text{H}_{13}\text{O}_2\text{NSCl}_2 \end{array}$	2.0	15	15	11-9	1.07	0.13	142-143	5.66	5.76	28.53	28.80	13.20	13.16
		3.0	20	35	11-7	0.750	traces							
		3.0	20	15	18-10	1.0	traces							
4	$\begin{array}{c} \text{n-C}_8\text{H}_7\text{SO}_2\text{NH}-\text{C}_6\text{H}_4-\text{Cl} \\ \text{C}_{11}\text{H}_{17}\text{O}_2\text{NSCl}_2 \end{array}$	2.0	20	30	20-8	0.25	traces	95-96	5.25	5.44	27.28	27.23	12.33	12-45
		2.0	15	20	13-9	0.25	0.2							
		2.0	15	15	14-8	1.0	0.01							

TABLE 2

Serial No.	Formula of the compound	Taken initially		Yield of products		M.p.	% N		% Br		% S	
		p-Phen- diide (in g)	Bromine (in ml)	Dichloro- roethane (in ml)	(in g)	(in %)	found	calc.	found	calc.	found	calc.
1	$\begin{array}{c} \text{Br} \\   \\ \text{CH}_3\text{SO}_2\text{NH}-\text{C}_6\text{H}_3-\text{OC}_2\text{H}_5 \\   \\ \text{Br} \\ \text{C}_{12}\text{H}_{11}\text{O}_4\text{NSBr}_2 \end{array}$	0.7	0.4	18	0.7	58.0	3.62	3.75	43.0	42.89	8.50	8.57
2	$\begin{array}{c} \text{Br} \\   \\ \text{C}_2\text{H}_5\text{SO}_2\text{NH}-\text{C}_6\text{H}_3-\text{OC}_2\text{H}_5 \\   \\ \text{Br} \\ \text{C}_{12}\text{H}_{10}\text{O}_4\text{NSBr}_2 \end{array}$	1.0	0.5	20	1.1	65.08	3.54	3.61	41.21	41.34	8.30	8.26
3	$\begin{array}{c} \text{Br} \\   \\ n\text{-C}_4\text{H}_9\text{SO}_2\text{NH}-\text{C}_6\text{H}_3-\text{OC}_2\text{H}_5 \\   \\ \text{Br} \\ \text{C}_{17}\text{H}_{20}\text{O}_4\text{NSBr}_2 \end{array}$	2.0	0.9	22	1.7	51.5	3.28	3.41	40.12	39.02	7.59	7.8
4	$\begin{array}{c} \text{Br} \\   \\ n\text{-C}_4\text{H}_9\text{SO}_2\text{NH}-\text{C}_6\text{H}_3-\text{OC}_2\text{H}_5 \\   \\ \text{Br} \\ \text{C}_{17}\text{H}_{19}\text{O}_4\text{NSBr}_2 \end{array}$	1.0	0.5	20	1.0	61.11	3.30	3.37	38.41	38.55	7.73	7.71

dichlorophenetidine of ethanesulfonic acid and tetrachlorobenzoquinone in acetone was used. The solution was added in drops from a separating funnel to the adsorbent and slowly drawn through. The upper layers of the adsorbent were colored yellow, and the lower layer became slightly pink. Elution was carried out first with acetone, on which the yellow upper layer of quinone moved slightly and became more concentrated but was not eluted; the acetone eluate was evaporated. Snow-white crystals of the dichlorophenetidine were obtained. Yield 0.25 g.

The quinone zone was eluted with benzene. After evaporating the benzene solution, the quinone was obtained in the form of pale brown flakes.

Bromination of the alkanesulfon-p-phenetidides (Table 2). The calculated amount of bromine in solution in dichloroethane was added in small portions to a dichloroethane solution of the p-phenetidine with stirring. After some time, the abundant evolution of hydrogen bromide was observed. On the following day, the reaction mixture was poured into an evaporating dish. After the evaporation of the dichloroethane, a viscous reddish oil remained, from which, on washing with cold alcohol, a microcrystalline residue of the 2,5-dibromo-p-phenetidine separated. It was recrystallized from hot alcohol.

Hydrolysis of the dihalogenoalkanesulfon-p-phenetidides was carried out by the method described earlier [1] with sulfuric acid diluted 1:3, since resinification of the product took place with more concentrated acid.

The results of the individual experiments on the halogenation of the alkanesulfon-p-phenetidides are given in Tables 1 and 2.

#### SUMMARY

The chlorination and bromination of methane-, ethane-, propane-, and butanesulfon-p-phenetidides have been studied. It has been shown that the reaction goes with the formation of the 2,5-dihalogeno derivatives, tetrachlorobenzoquinone being formed as a by-product with the dichlorophenetidine in the case of chlorination.

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# THE STRUCTURE OF THE CONDENSATION PRODUCTS OF 4,4'-DIHYDROXYLDIPHENYL SULFONE WITH FORMALDEHYDE

Ya. P. Berkman and L. M. Shuter

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4,4'-Dihydroxydiphenyl sulfone is used as a component of the phenol-formaldehyde condensation. Having four reactive positions in the molecule it may form various condensation products with formaldehyde according to the reaction conditions, the quantitative ratios of the reactants, and the catalyst chosen. The patent literature indicates the possibility of using the condensation products as synthetic tanning agents, lacquers, and cation-exchange resins [1].

In contrast to phenol and its homologs, for which the process itself and the condensation products have been subjected repeatedly to detailed investigation, the condensation of dihydroxydiphenyl sulfone with formaldehyde remains almost completely uninvestigated, and the structure of the products unelucidated.

With respect to the type of internuclear bond, the following assumptions have been expressed:

- (1) Bond through methylene- $\text{CH}_2$ -groups-of the type of a diarylmethane [2],
- (2) bond through- $\text{CH}_2\text{OCH}_2$ -groups-of the type of dibenzyl ether [3],
- (3) bond through ether- $\text{OCH}_2\text{O}$ -bridges between the phenyl hydroxyl groups [4].

Not one of these hypotheses has direct experimental evidence and they are based predominantly on analogies.

In order to elucidate the question, we have carried out an investigation of the condensation products of dihydroxydiphenyl sulfone with formalin—a sulfone resin—by separating it into narrow fractions and analysing the individual fractions. The mean molecular weights were determined by isothermal distillation, the content of hydroxyl groups by acylation with acetic anhydride, and the bromine number by the bromide-bromate method; and the viscosities were determined in alcoholic solution. To confirm the conclusions at which we arrived, we carried out independent syntheses of some compounds.

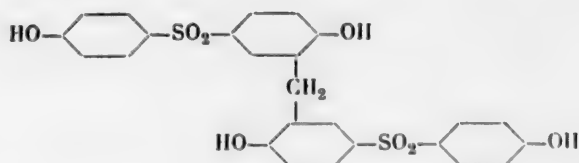
As subject of the study, the product of the "complete" condensation was taken, i.e., the resin obtained in an acid medium. In consideration of the diminished reactivity of the sulfone, the reaction was carried out under pressure at  $140^\circ$  for 3 hours. The ratio of sulfone to formaldehyde in g-mole was 1.00:0.75. The resin was separated into 12 fractions by precipitation with water from alcoholic solution. The results of the analysis of these fractions are given in Table 1.

It can be seen from the data of Table 1 that the content of hydroxyl groups does not display any considerable differences, and the bromine number diminishes as the mean molecular weight rises. These results show that the hydroxyl groups of sulfone are preserved in all the fractions of the condensation products. Thus, structure "3"—bond through ether bridges between phenolic hydroxyl groups [4] is impossible.

In order to decide between structures "1" and "2", i.e., the diarylmethane and the dibenzyl ether types, the reaction with hydrogen bromide was used. As is well known, dibenzyl ethers readily react with hydrogen bromide with rupture of the ethereal linkage and the formation of the corresponding bromides; this reaction can be used for their quantitative determination [5]. It was found that in the action of hydrogen bromide on the resin its molecular weight remained unchanged, i.e., no rupture of the chain took place; this indicates the absence of dibenzyl ether groups in the resin and excludes the possibility of assuming structure "2".

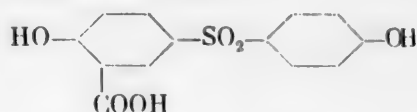
Thus, the methylene internuclear link is the only possible one completely agreeing with the analytical data: the condensation products can only be of the diarylmethane type.

For complete confirmation of the conclusions indicated, it was desirable to isolate the simplest possible condensation product: methylene-bis-3-(4,4'-dihydroxydiphenyl sulfone).



A colorless substance of microcrystalline structure, insoluble in hot water and with m.p. 290°, was obtained from fraction No. 11 by fractional crystallization. In respect of its analytical data, it corresponded completely with the formula shown (Table 2).

Since methylene-bis-3-(4,4'-dihydroxydiphenyl sulfone) has not hitherto been described in the literature, it was synthesized in high yield starting from 4,4'-dihydroxy-3-hydroxymethyldiphenyl sulfone [6] by boiling with a tenfold excess of 4,4'-dihydroxydiphenyl sulfone in an alkaline solution. It formed a crystalline material, insoluble in hot water, with m.p. 297-299°. The structure of methylene-bis-3-(4,4'-dihydroxydiphenyl sulfone) was shown by acetylation with acetic anhydride to form methylene-bis-3-(4,4'-diacetoxydiphenyl sulfone) and by oxidation with potassium permanganate to a mixture of 4,4'-dihydroxy-3-carboxydiphenyl sulfone



and the initial 4,4'-dihydroxydiphenyl sulfone.

A comparison of the synthesized sample of methylene-bis-3-(4,4'-dihydroxydiphenyl sulfone) with the product isolated from the 11th fraction established their identity. A mixture of the two substances showed no depression of the melting point.

It follows from what has been said that the condensation of dihydroxydiphenyl sulfone with formaldehyde leads to products having a structure completely analogous to that of the condensation products of phenol and its homologs. The production of methylene-bis-3-(4,4'-dihydroxydiphenyl sulfone) by the condensation of the sulfone with its hydroxymethyl derivative permits the conclusion that the mechanism of the two reactions is completely analogous.

TABLE 2

	Found	Calculated
Molecular weight .....	504	512
% OH .....	13.32	13.27
Bromine number .....	193	187

#### EXPERIMENTAL PART

**Methylene-bis-3-(4,4'-dihydroxydiphenyl sulfone).** A mixture of 2.8 g of 4,4'-dihydroxy-3-hydroxymethyldiphenyl sulfone (0.01 g-mole) and 25 g of 4,4'-dihydroxydiphenyl sulfone (0.1 g-mole) was dissolved with heating in 50 ml of 5% NaOH solution. The solution was boiled in a flask with a reflux condenser for 12 hours. After acidification with sulfuric acid, a product insoluble in boiling water was obtained. Yield 4 g. It formed fine crystalline prisms with m.p. 297-298° (from 30% alcohol). The melting point, it was found, had to be determined in a metal block provided with a thermocouple [7], since on slow heating in a capillary decomposition of the substance took place before the melting point was reached. An alcoholic solution of the substance gave a violet color with FeCl<sub>3</sub>.

Found %: C 58.38; H 4.07; S 12.60; OH 13.37. M 537 (isothermal distillation in acetone).  $C_{25}H_{20}O_8S_2$ . Calculated %: C 58.60; H 3.93; S 12.51; OH 13.27. M 512.

**Acetylation.** On boiling methylene-bis-(dihydroxydiphenyl sulfone) with an excess of acetic anhydride, methylene-bis-3-(4,4'-diacetoxydiphenyl sulfone) with m.p. 165-166° (after recrystallization from alcohol) was obtained.

Found %: C 58.52; S 9.55. M 654 (isothermal distillation in acetone).  $C_{33}H_{20}O_{12}S_2$ . Calculated %: C 58.20; S 9.42. M 681.

**Oxidation.** To a solution of 1 g of methylene-bis-(dihydroxydiphenyl sulfone) in 10 ml of 10% NaOH solution, 30 ml of 5% potassium permanganate solution was added with vigorous stirring. The excess of permanganate and the manganate were reduced by adding sodium sulfite. After separation from the manganese dioxide, the solution was acidified with sulfuric acid. The product which separated was extracted in the cold with a solution of sodium bicarbonate, acidified, and recrystallized from hot water. Crystals were obtained which were identified as 4,4'-dihydroxy-3-carboxydiphenyl sulfone; m.p. 230-231°, giving no depression with the pure substance; with  $FeCl_3$  a red color is formed. Yield about 30%. The part insoluble in bicarbonate consisted of 4,4'-dihydroxydiphenyl sulfone: M.p. 247-248°, giving no depression with the pure material; with  $FeCl_3$  it forms a red-violet color.

#### SUMMARY

1. It has been established that in the condensation of 4,4'-dihydroxydiphenyl sulfone with formaldehyde in an acid medium, linkage of the molecules of the sulfone through methylene groups of the diarylmethane type takes place, similar to the condensation of phenol and its homologs with formaldehyde. From a fraction with a mean molecular weight of 437 obtained by precipitation with water from an alcoholic solution of the condensation product, a crystalline product was obtained corresponding, with respect to analytical data, to methylene-bis-3-(4,4'-dihydroxydiphenyl sulfone), not described in the literature.

2. The structure of the methylene-bis-3-(4,4'-dihydroxydiphenyl sulfone) was shown by its independent synthesis from 4,4'-dihydroxy-3-hydroxymethyldiphenyl sulfone, by acetylation, and by oxidation.

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TRIPHENYLPHOSPHAZOAROYL, N-DIPHENYLPHOSPHINYL PHENYL ARYL KETIMINES, AND N-DIARYLEPHOSPHINYLAROYLAMIDES .

G. I. Derkach, E. S. Gubnitskaya, and A. V. Kirsanov

The Institute of Organic Chemistry of the Academy of Sciences of the Ukrainian SSR

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Triphenyl- and phenyldiethylphosphazobenzoyls were obtained by Staudinger [1] by the action of the corresponding tertiary phosphines on the azide of benzoic acid.



The triarylphosphazobenzoyls,  $\text{ArSO}_2\text{N}=\text{PAR}'_3$ , were obtained by the action of arylmagnesium bromides on trichlorophosphazobenzoyls [2] and by the reaction of amides of aryl sulfonic acids with dichlorotriarylphosphoranes [3].



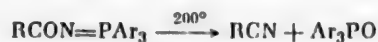
Attempts to use the last reaction to obtain triphenylphosphazobenzoyls met with no success, since the reaction did not stop at the stage of the phosphazobenzoyls—the splitting out of a tertiary phosphine oxide and the formation of nitriles took place immediately [3, 4].



Triphenylphosphazobenzoyls have been obtained successfully by the action of phenylmagnesium bromide on trichlorophosphazobenzoyls.



The triphenylphosphazobenzoyls (Table 1) are colorless crystalline substances which remain unchanged on protracted boiling (~ 6 hours) with dilute solutions of acids or alkalis. On heating to 200°, they decompose into carboxylic acid nitriles and tertiary phosphine oxides (see [1, 5]).



The action of phenylmagnesium bromide on the chlorides of N-dichlorophosphinyliminocarboxylic acids leads to N-diphenylphosphinyl phenyl aryl ketimines isomeric with the triphenylphosphazobenzoyls.



The N-diphenylphosphinyl phenyl aryl ketimines (Table 1) are viscous heavy oils which cannot be distilled in vacuum without decomposition. On prolonged boiling with dilute solutions of alkalis or acids, they do not change.

The reaction of phenyllithium or phenyl magnesium bromide with the acid chloride of N-diphenoxyphosphinyliminobenzoic acid yields N-diphenoxyphosphinyl diphenyl ketimines, which form colorless crystalline substances stable to saponification by dilute acids and alkalis.



The dichlorides of N-aryolphosphoramidic acids are readily arylated by the action of arylmagnesium bromides to form N-(diarylphosphinyl)-arylamides (N-arylamides of diarylphosphinic acids)



The N-(diarylphosphinyl)-arylamides are colorless crystalline substances (Table 2) possessing the properties of weak acids. They are soluble in dilute aqueous solutions of alkali but are insoluble in dilute aqueous solutions of acids.

TABLE 1. Triphenylphosphazaroaryls of the Type  $\text{ArCON}=\text{P}(\text{C}_6\text{H}_5)_3$ \*

Ar	Yield (%)	M.p.	External form, crystallizing solvent	Found, %	Empirical formula	Calc., %
$\text{C}_6\text{H}_5$ **	80	192—193°	Needles, ethanol	N 3.62, 3.71	$\text{C}_{25}\text{H}_{20}\text{ONP}$	N 3.68
p- $\text{ClC}_6\text{H}_4$	81	54—56	Prisms, benzene + petroleum ether	P 7.39, 7.36	$\text{C}_{25}\text{H}_{19}\text{ONPCL}$	P 7.45
p- $\text{BrC}_6\text{H}_4$	85	100 (dec.)	Plates, benzene + petroleum ether	P 7.09, 7.06	$\text{C}_{25}\text{H}_{19}\text{ONPBr}$	P 6.73

N-Diphenylphosphinyl phenyl aryl ketimines of the type  $\text{ArC}[\text{=NPO}(\text{C}_6\text{H}_5)_2]\text{C}_6\text{H}_5$ \*

$\text{C}_6\text{H}_5$	98	—	Heavy liquid***	P 8.12, 8.17 N 3.41	$\text{C}_{25}\text{H}_{20}\text{ONP}$	P 8.12 N 3.68
p- $\text{ClC}_6\text{H}_4$	70	—	Heavy liquid***	P 7.40, 7.12	$\text{C}_{25}\text{H}_{19}\text{ONPCL}$	P 7.45
p- $\text{BrC}_6\text{H}_4$	80	—	Heavy liquid***	P 6.63, 6.53 Br 16.98, 16.96	$\text{C}_{25}\text{H}_{19}\text{ONPBr}$	P 6.73 Br 17.28

N-(diarylphosphinyl)-arylamides are very stable to hydrolysis, not changing on prolonged boiling with dilute acids or alkalis. By thermal decomposition, they give nitriles and diarylphosphinic acids [see 1, 5] (Table 3).



In the action of phosphorus pentachloride on the N-phosphinyl derivatives of arylamides, the direction of the reaction depends on the nature of the substituents in the phosphinyl group—N-(dichlorophosphinyl)- and N-(diaryloxyphosphinyl)-arylamides [6] give the chlorides of the corresponding N-phosphinyl derivatives of iminocarboxylic acids.



The N-(dianilinophosphinyl)-arylamides are decomposed by the action of phosphorus pentachloride [7] into nitriles and chlorides of phosphorodanilidic acids.



\* All the substances were insoluble in water and petroleum ether, sparingly soluble in ether, acetone, and carbon tetrachloride, and readily soluble in benzene alcohol.

\*\* A method of obtaining this substance from triphenylphosphine and benzoic acid azide is given in the literature [1].

\*\*\* Purified by repeated reprecipitation from benzene solution with petroleum ether.

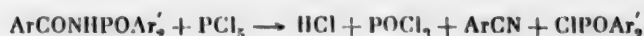
TABLE 2. N-(Diarylphosphiny)-arylamides of the Type  $\text{ArCONHPOAr}_2$ 

Ar	Ar'	Yield (%)	M.p.	External form, crystallizing solvent	Found, %	Empirical formula	Calc., %	Solubility*					
$\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$	72	149—151°	Prisms, ethanol + petroleum ether	N 4.12, 4.03 P 9.24, 9.17	$\text{C}_{19}\text{H}_{16}\text{O}_2\text{NP}$	N 4.36 P 9.64	+	+	+	+	+	+
$\text{C}_6\text{H}_5$	$p\text{-CH}_3\text{C}_6\text{H}_4$	72	224—225	Prisms, benzene + petroleum ether	P 8.70, 8.61	$\text{C}_{21}\text{H}_{20}\text{O}_2\text{NP}$	P 8.82	+	+	+	+	+	+
$\text{C}_6\text{H}_5$	$p\text{-BrC}_6\text{H}_4$	70	187—188	Needles, ethanol	P 6.34, 6.20	$\text{C}_{19}\text{H}_{14}\text{O}_2\text{NPBr}_2$	P 6.47	+	+	+	+	+	+
$o\text{-ClC}_6\text{H}_4$	$\text{C}_6\text{H}_5$	80	92—94	Prisms, benzene + petroleum ether	N 3.95, 4.03 P 9.69	$\text{C}_{19}\text{H}_{15}\text{O}_2\text{NPCl}$	N 3.94 P 9.97	+	+	+	+	+	+
$p\text{-ClC}_6\text{H}_4$	$\text{C}_6\text{H}_5$	95	204—205	Fine prisms, methanol	N 4.00, 3.82	$\text{C}_{19}\text{H}_{15}\text{O}_2\text{NPCl}$	N 3.94	+	+	+	+	+	+
$p\text{-ClC}_6\text{H}_4$	$p\text{-CH}_3\text{C}_6\text{H}_4$	71	208—209	Needles, ethanol	P 7.54, 7.59 Cl 10.41, 10.21	$\text{C}_{21}\text{H}_{19}\text{O}_2\text{NPCl}$	P 7.53 Cl 10.36	+	+	+	+	+	+
$p\text{-BrC}_6\text{H}_4$	$p\text{-BrC}_6\text{H}_4$	52	205—207	Prisms, dioxane + petroleum ether	P 6.67, 6.77	$\text{C}_{19}\text{H}_{13}\text{O}_2\text{NPBr}_2$	P 6.03	+	+	+	+	+	+
$o\text{-BrC}_6\text{H}_4$	$\text{C}_6\text{H}_5$	70	167—168	Plates, 70% ethanol	P 7.48, 7.38	$\text{C}_{19}\text{H}_{15}\text{O}_2\text{NPBr}$	P 7.74	+	+	+	+	+	+
$p\text{-BrC}_6\text{H}_4$	$\text{C}_6\text{H}_5$	88	208—209	Prisms, methanol	P 3.49, 3.29 Br 19.76, 19.74	$\text{C}_{19}\text{H}_{15}\text{O}_2\text{NPBr}$	N 3.50 Br 19.96	+	+	+	+	+	+
$p\text{-BrC}_6\text{H}_4$	$p\text{-BrC}_6\text{H}_4$	65	204—206	Prisms, 70% ethanol	P 5.48, 5.25	$\text{C}_{19}\text{H}_{13}\text{O}_2\text{NPBr}_3$	P 5.56	+	+	+	+	+	+

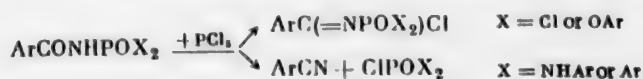
\* Symbols: † readily soluble at 20°, + readily soluble at the boil, — sparingly soluble at the boil, = insoluble at the boil. All substances are insoluble in water and petroleum ether, and sparingly soluble in ether.



The N-(diarylphosphinyl)-arylamides react with phosphorus pentachloride analogously to the N-(dianilidophosphinyl)-arylamides, with the formation of nitriles of aromatic acids and chlorides of diarylphosphinic acids (Table 4).



Thus, more highly electronegative substituents in the phosphinyl group (Cl, OAr) favor the formation of chlorides of N-phosphinyl derivatives of iminoacids and less highly electronegative substituents (NHAr, Ar) the splitting of the molecule into nitriles of aromatic acids and chlorides of the corresponding derivative of phosphoric acid.



The chlorides of the diarylphosphinic acids were isolated in the form of anilides or in the form of the free diarylphosphinic acids and were identified by the mixed melting point test. The nitriles were isolated as such.

TABLE 3. Yields of Products of the Thermal Decomposition of diphenylphosphinylarylamides of the Type  $\text{ArCONHPO}(\text{C}_6\text{H}_5)_2$

Ar	$\text{C}_6\text{H}_5$	p- $\text{ClC}_6\text{H}_4$	p- $\text{BrC}_6\text{H}_4$
Yield %	50	58	64
ArCN	71	70	66

## EXPERIMENTAL PART

Triphenylphosphazaroaroyls (Table 1). A solution of 0.035 g-mole of trichlorophosphazaroaroyl in 150 ml of anhydrous benzene was added to a solution of 0.15 g-mole of phenylmagnesium bromide in 100 ml of ether, with vigorous stirring and cooling with ice water. A colorless crystalline precipitate gradually separated. The reaction mixture was boiled under a reflux condenser for 2 hours and left to stand for 12 hours at

20°. The crystalline precipitate was filtered off with suction, washed with benzene (2 × 20 ml) and ether (2 × 20 ml), and the filtrate was evaporated in vacuum. The residue contained the triphenylphosphazaroaroyl in the form of a colorless crystalline mass, or a viscous oil which slowly crystallized on washing with water and rubbing with a glass rod. The crystals were filtered off with suction, dried, and recrystallized.

TABLE 4. Yields of Products of the Reaction of N-(diarylphosphinyl)-arylamides of the Type of  $\text{ArCONHPOAr}'_2$  with Phosphorus Pentachloride

Ar Ar'	$\text{C}_6\text{H}_5$ $\text{C}_6\text{H}_5$	$\text{C}_6\text{H}_5$ p- $\text{ClC}_6\text{H}_4$	p- $\text{ClC}_6\text{H}_4$ $\text{C}_6\text{H}_5$	p- $\text{BrC}_6\text{H}_4$ $\text{C}_6\text{H}_5$
Yield %	79 [8]	85*	80 [8]	71 [8]
$\text{C}_6\text{H}_5\text{NHPOAr}'_2$	87	—	—	71
ArCN	60 [9]	—	—	85 [9]

N-Diphenylphosphinyl phenyl aryl ketimines (Table 1) were obtained in a similar manner to the triphenylphosphazaroaroyls by the action of phenylmagnesium bromide on chlorides of N-(dichlorophosphinyl)-iminocarboxylic acids. They were purified by repeated reprecipitation from benzene solution with petroleum ether.

N-Diphenoxyphosphinyl diphenyl ketimines. A solution of 0.02 g-mole of the chloride of N-diphenoxyphosphinyliminobenzoic acid in 30 ml of anhydrous benzene was added to a solution of 0.025 g-mole of phenyllithium in 30 ml of ether in an atmosphere of nitrogen with vigorous stirring and cooling at such a rate that the temperature of the reaction mixture did not rise above 5° which took 40-50 minutes. The reaction mixture was boiled for 30 minutes and left to stand at room temperature for 12 hours. The precipitate which separated was filtered off with suction and washed with ether (2 × 15 ml) and the filtrate was evaporated in vacuum. The residue was a glassy mass which gradually crystallized on treatment with petroleum ether. The crystals were filtered off with suction, washed, and recrystallized from alcohol. Yield 28%. N-Diphenoxyphosphinyl diphenyl ketimine forms colorless prisms, readily soluble in dioxane, sparingly soluble in benzene and ether, and insoluble in petroleum ether and water, m.p. 184-185°.

Found %: N 3.23, 3.35. P 7.00.  $\text{C}_{25}\text{H}_{29}\text{O}_3\text{NP}$ . Calculated %: N 3.39, P 7.49.

The same product was obtained by the action of phenylmagnesium bromide on the chloride of N-diphenoxyphosphinyliminobenzoic acid with a yield of 15%.

N-(Diarylphosphinyl)-arylamides (Table 2). A solution of 0.03 g-mole of the dichloride of a N-aryolphosphoramidic acid in 150-200 ml of anhydrous dioxane was added to a solution of 0.1 g-mole of an arylmagnesium bromide in 80 ml of ether with vigorous stirring and cooling with ice water. The reaction mixture was stirred at room temperature for 3 hours and left to stand for 12 hours. The crystalline residue was filtered off with suction, and washed with dioxane (2 × 20 ml) and ether (2 × 20 ml) and the filtrate was evaporated in vacuum. The residue contained the diarylphosphinylarylamides in the form of a viscous oil which gradually crystallized on treatment with alcohol or petroleum ether. The crystals were filtered off with suction, dried, and recrystallized.

Thermal decomposition of the diphenylphosphinylarylamides (Table 3). The diphenylphosphinylarylamide (0.1 g-mole) was slowly heated to 190-210°. The decomposition was complete after 1-2 minutes. The dark brown reaction mixture was cooled to room temperature and 0.5 N aqueous caustic soda was added until an alkaline reaction to phenolphthalein was given. The nitriles of the carboxylic acids were extracted with ether and purified by the usual methods. The alkaline solution was treated with active carbon and filtered, and the filtrate was acidified with concentrated hydrochloric acid to Congo red. The crystals of diphenylphosphinic acid which separated were filtered off with suction, dried, and crystallized. They were identified by mixed melting point tests.

The reaction of N-(diarylphosphinyl)-arylamides with phosphorus pentachloride without a solvent took place explosively.

A. Isolation of the anilides of diarylphosphinic acids (Table 4). A mixture of 0.01 g-mole of N-(diarylphosphinyl)-arylamide, 20 ml of benzene, and 0.011 g-mole of phosphorus pentachloride was boiled with a reflux condenser until the evolution of hydrogen chloride ceased (15-20 minutes). The solvent and the phosphoryl chloride were distilled off in vacuum and the residue was dissolved in 25 ml of benzene, and a mixture of 0.02 g-mole of aniline and 10 ml of benzene was added to the solution with stirring and cooling in ice water. The precipitate which separated was filtered off with suction, washed with water (2 × 30 ml), and recrystallized. Identification was carried out by the mixed melting point test.\*

B. Isolation of nitriles and diarylphosphinic acids (Table 4). After carrying out the reaction and distilling off the benzene and the phosphoryl chloride in vacuum, as described above, a 0.5 N solution of caustic soda was added to the residue until an alkaline reaction to phenolphthalein was obtained. The nitriles were extracted with ether, purified, and identified by the usual methods, and the aqueous solution was acidified with hydrochloric acid to Congo red. The diarylphosphinic acid separating out was filtered off with suction, washed, and recrystallized.

#### SUMMARY

1. The action of phenylmagnesium bromide on trichlorophosphazaroaroyls yields triphenylphosphazaroaroyls.
2. The reaction of chlorides of N-(dichlorophosphinyl)-iminocarboxylic acids with phenylmagnesium bromide gives N-diphenylphosphinyl phenyl aryl ketimines.
3. The action of arylmagnesium bromides on dichlorides of phosphoroarylamidic acids yields N-(diarylphosphinyl)-arylamides.
4. The reaction of phosphorus pentachloride with N-(diarylphosphinyl)-arylamides forms chlorides of diarylphosphinic acids and the nitriles of the corresponding carboxylic acids.
5. The direction of the reaction of phosphorus pentachloride with compounds of the type  $\text{ArCONHPOX}_2$  depends on the nature of the group X. If X is Cl or OAr, the chlorides of the corresponding N-phosphinyl derivatives of iminoacids are obtained. If X is NHAr or Ar, nitriles of aromatic acids and chlorides of the corresponding di-substituted phosphonic acids are obtained.

\* The anilide of di-p-tolylphosphinic acid forms prisms (from benzene), m.p. 160-161°, readily soluble in boiling dioxane and benzene, sparingly soluble in ether and carbon tetrachloride, and insoluble in water and petroleum ether.

Found %: P 9.80, 9.81.  $\text{C}_{20}\text{H}_{20}\text{ONP}$ . Calculated %: P 9.82.

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# PHENYLDICHLOROPHOSPHAZOARYLS

I. N. Zhmurova and A. V. Kirsanov

The Institute of Organic Chemistry of the Academy of Sciences of the Ukrainian SSR

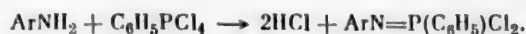
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 11,

pp. 3685-3689, November, 1961

Original article submitted December 2, 1960

Compounds of the type  $\text{ArN}=\text{PX}_3$  exist in the monomeric or the dimeric state according to the nature of the aryl residue bound to the nitrogen atom [1] and the nature of the substituents bound to the phosphorus atom. The more electronegative the substituents X, the more readily does the molecule dimerize; the majority of trichlorophosphazoyls  $\text{ArN}=\text{PCl}_3$  are dimeric [1], while the triphenylphosphazoyls  $\text{ArN}=\text{P}(\text{C}_6\text{H}_5)_3$  [2] and triphenoxyphosphazoyls  $\text{ArN}=\text{P}(\text{OC}_6\text{H}_5)_3$  [3] are monomeric. It was of interest to determine how the partial substitution of the chlorine atoms in trichlorophosphazoyls by less negative substituents, for example, phenyl, would affect the tendency of the molecule  $\text{ArN}=\text{PX}_3$  to dimerize.

For this purpose, a series of phenyldichloroazoyls,  $\text{ArN}=\text{P}(\text{C}_6\text{H}_5)\text{Cl}_2$  (Table) was synthesized by the method of the first phosphazo reaction [4] by the reaction of aromatic amines or their hydrochlorides with phenyltetrachlorophosphorane.



As in the case of phosphorus pentachloride [1], the reaction proceeds with good yields under mild conditions—on boiling in carbon tetrachloride.

The physical and chemical properties of the phenyldichlorophosphazoyls obtained from amines with a low basicity ( $K_{\text{base}} < 1 \cdot 10^{-10}$ , compounds 7-21 in the Table) are close to the physical and chemical properties of the monomeric trichlorophosphazoyls [1]—they have a relatively low melting point or are liquids and are very soluble in the usual nonpolar organic solvents (benzene, carbon tetrachloride, chloroform, dioxane). Like the monomeric trichlorophosphazoyls, they are extremely readily hydrolyzed by water and atmospheric moisture. On boiling with water, the phenyldichlorophosphazoyls decompose into phenylphosphinic acid, hydrogen chloride, and the initial amine, but a small amount of resinous or amorphous by-products is also formed. Hence, determination of the equivalent after hydrolysis of phenyldichlorophosphazoyls gives somewhat low results (3.4-3.9 equiv. instead of 4). The phenyldichlorophosphazoyls 1-6 obtained from amines of relatively high basicity ( $K_{\text{base}}$  of the order of  $1 \cdot 10^{-9}$ – $1 \cdot 10^{-10}$ ) differ from the other compounds in their properties. They are very sparingly soluble at room temperature in the usual nonpolar organic solvents. Further, on boiling, they dissolve in the same solvents extraordinarily readily and precipitate from the cooled solutions very slowly. Thus, for example, 0.1-0.2 g of compounds 1-4 dissolves in 20 ml of benzene after stirring at 20° for 20-30 minutes. Compounds 5 and 6 are even more sparingly soluble. On boiling in 20 ml of benzene, 20-30 g of compounds 1-6 dissolves readily. After cooling the solution, crystallization sets in very slowly—after several hours or after a day. Compounds 1 and 3-6 separate out in the crystalline state only from very concentrated solutions (20-30 g in 20-25 ml of benzene or carbon tetrachloride). Crystallization does not occur completely or does not set in at all from more dilute solutions. Compound 2 crystallizes only after complete removal of the solvent. The phenyldichlorophosphazoyls 1-6 are distinguished from the remainder also by their chemical properties. By the action of formic or acetic acid, all the phenyldichlorophosphazoyls are converted into chlorides of phenylphosphinanilidic acid  $\text{ArNHPOClC}_6\text{H}_5$ . Acidolysis was carried out in benzene solution at room temperature. The reaction can be carried out readily for compounds 1-6 as well, since they, as mentioned above, readily dissolve in benzene on heating and crystallize out very slowly on cooling.

The action of formic acid or acetic acid on compounds 1-6 in the crystalline state (suspension in benzene) forms very low-melting crystalline compounds which do not contain chlorine, the structure of which has not yet been determined, and the chlorides of phenylphosphinanilidic acids are not formed at all. Thus, the phenyldichlorophosphazoyls 1-6, in respect of their physical and chemical properties, are reminiscent of the dimeric trichlorophosphazoyls

Phenyldichlorophosphazoyls  $\text{ArN} = \text{PCl}_2\text{C}_6\text{H}_5$

serial no.	Ar	yield (%)	M.p.	External form, crystallizing solvent	Empirical formula	Found		Calc.	
						% Cl	Molecular wt.	% Cl	Molecular weight
1	$\text{C}_6\text{H}_5$	72	119–120°	Colorless prisms	$\text{C}_{12}\text{H}_{10}\text{NCl}_3\text{P}$	25.81, 25.91	267, 287	26.29	270
2	m- $\text{CH}_3\text{C}_6\text{H}_4$	99	82–84	Ditto	$\text{C}_{13}\text{H}_{12}\text{NCl}_3\text{P}$	24.53, 24.72		25.00	
3	p- $\text{CH}_3\text{C}_6\text{H}_4$	85	124–126	Ditto	$\text{C}_{13}\text{H}_{12}\text{NCl}_3\text{P}$	24.88, 24.52	304, 284	25.00	284
4	p- $\text{ClC}_6\text{H}_4$	83	87–89	Ditto	$\text{C}_{12}\text{H}_9\text{NCl}_3\text{P}$	22.83, 22.73	297, 263	23.02	304.5
5	p- $\text{CH}_3\text{OC}_6\text{H}_4$	83	121–123	Ditto	$\text{C}_{13}\text{H}_{12}\text{ONCl}_3\text{P}$	23.11, 23.35		23.66	
6	p- $\text{C}_2\text{H}_5\text{OC}_6\text{H}_4$	81	92–94	Ditto	$\text{C}_{14}\text{H}_{14}\text{ONCl}_3\text{P}$	22.29, 22.57		22.61	
7	o- $\text{CH}_3\text{C}_6\text{H}_4$	95	Liquid	Heavy oil	$\text{C}_{13}\text{H}_{12}\text{NCl}_3\text{P}$	24.83, 24.74		25.00	
8	o- $\text{ClC}_6\text{H}_4$	97	"	Ditto	$\text{C}_{12}\text{H}_9\text{NCl}_3\text{P}$	23.23, 23.24	288, 273	23.02	304.5
9	m- $\text{ClC}_6\text{H}_4$	94	"	Ditto	$\text{C}_{12}\text{H}_9\text{NCl}_3\text{P}$	23.31, 23.42	291, 310	23.02	304.5
10	2,4- $\text{Cl}_2\text{C}_6\text{H}_3$	98	55–58	Colorless needles	$\text{C}_{12}\text{H}_8\text{NCl}_4\text{P}$	21.17, 21.28		20.94	
11	2,4,6- $\text{Cl}_3\text{C}_6\text{H}_2$	96	68–70	Colorless needles, from petroleum ether	$\text{C}_{12}\text{H}_7\text{NCl}_5\text{P}$	19.25, 19.03		19.01	
12	o- $\text{BrC}_6\text{H}_4$	91	Liquid	Heavy oil	$\text{C}_{12}\text{H}_9\text{NCl}_2\text{BrP}$	20.68, 20.30		20.34	
13	m- $\text{BrC}_6\text{H}_4$	93	"	Ditto	$\text{C}_{12}\text{H}_9\text{NCl}_2\text{BrP}$	20.35, 20.35		20.34	
14	p- $\text{BrC}_6\text{H}_4$	96	58–61	Colorless needles	$\text{C}_{12}\text{H}_9\text{NCl}_2\text{BrP}$	19.86, 20.00		20.34	
15	2,4- $\text{Br}_2\text{C}_6\text{H}_3$	93	94–96	Colorless needles	$\text{C}_{12}\text{H}_8\text{NCl}_2\text{Br}_2\text{P}$	16.29, 16.32		16.59	
16	2,4,6- $\text{Br}_3\text{C}_6\text{H}_2$	98	Liquid	Yellow oil	$\text{C}_{12}\text{H}_7\text{NCl}_2\text{Br}_3\text{P}$	13.97, 14.17		14.00	
17	o- $\text{O}_2\text{NC}_6\text{H}_4$	94	48–50	Pale yellow prisms	$\text{C}_{12}\text{H}_9\text{O}_2\text{N}_2\text{Cl}_3\text{P}$	22.55, 22.00		22.54	
18	m- $\text{O}_2\text{NC}_6\text{H}_4$	99	Liquid	Yellow oil	$\text{C}_{12}\text{H}_9\text{O}_2\text{N}_2\text{Cl}_3\text{P}$	22.26, 21.97		22.54	
19	p- $\text{O}_2\text{NC}_6\text{H}_4$	80	105–107	Pale yellow needles, from benzene	$\text{C}_{12}\text{H}_9\text{O}_2\text{N}_2\text{Cl}_3\text{P}$	22.18, 22.37		22.54	
20	2,4-( $\text{O}_2\text{N}$ ) $_2\text{C}_6\text{H}_3$	64	160–161	Pale yellow prisms, from benzene	$\text{C}_{12}\text{H}_8\text{O}_4\text{N}_2\text{Cl}_2\text{P}$	19.53, 19.84	330, 338	19.72	360
21	2,6- $\text{Cl}_2$ -4- $\text{O}_2\text{NC}_6\text{H}_2$	95	158–160	Pale yellow needles, from benzene or $\text{CCl}_4$	$\text{C}_{12}\text{H}_7\text{O}_2\text{N}_2\text{Cl}_4\text{P}$	18.13, 18.78		18.49	

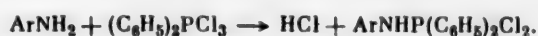
\* Cryoscopic in benzene.

\*\* Hydrolyzable chlorine.

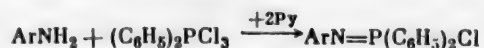
[1]. Determinations of the molecular weights of compounds 1, 3, and 4 cryoscopically in benzene showed that they are monomeric in benzene solution. However, on the basis of the physical and chemical properties, it may be assumed that, in the solid state, compounds 1-6 are dimeric. In contrast to the corresponding trichlorophosphazoyls, which form dimers difficult to dissociate [1], the dimers of the phenyldichlorophosphazoyls are very unstable and decompose into the monomers in benzene solution at room temperature. Increasing the temperature accelerates the monomerization; hence, on heating, the solubility increases several times. In benzene solution, the molecules of compounds 1-6 are completely monomerized; hence, acidolysis goes according to the usual scheme with the formation of chlorides of phenylphosphinanilidic acids. The dimeric trichlorophosphazoyls, on being monomerized by boiling in nonpolar solvents, react similarly with formic and acetic acids [1].

Thus the tendency to dimerize diminishes sharply on passing from trichlorophosphazoyls to phenyldichlorophosphazoyls, which confirms the correctness of the theoretical positions developed earlier [1, 3]. Only amines with very low basicity ( $K_{\text{base}} \leq 1 \cdot 10^{-14}$ ) give monomeric trichlorophosphazoyls by the action of phosphorus pentachloride; all the others form dimeric trichlorophosphazoyls [1]. And only amines with comparatively high basicity ( $K_{\text{base}}$  of the order of  $1 \cdot 10^{-9} - 1 \cdot 10^{-10}$ ), by reaction with phenyltetrachlorophosphorane, give phenyldichlorophosphazoyls which are dimeric in the crystalline state but readily dissociate into monomers on dissolution in nonpolar solvents.

Diphenyltrichlorophosphorane reacts with aromatic amines with the formation of quasi-phosphonium compounds.



If the reaction is carried out in the presence of tertiary bases (pyridine, triethylamine), diphenylchlorophosphazoyls are obtained.



## EXPERIMENTAL PART

Phenyldichlorophosphazoyls (table). A mixture of 0.1 g-mole of the hydrochloride of an aromatic amine or the free amine, 0.1 g-mole of phenyltetrachlorophosphorane, and carbon tetrachloride was boiled under reflux until the evolution of hydrogen chloride ceased (2-3 hours).

Compounds 1 and 3-6. The amount of carbon tetrachloride used was 15 ml. After cooling, the solution was filtered and left for a day at 20°, and the crystals which separated were filtered off, washed with carbon tetrachloride and benzene, and dried in vacuum.

Compounds 2 and 7-18. The amount of carbon tetrachloride taken was 50 ml. After completion of the reaction, the solvent was distilled off in vacuum. The residue was a heavy almost colorless oil. Compounds 2, 10, 11, 14, 15, and 17 crystallized on cooling and rubbing with a glass rod. Compound 15 was washed with a mixture of benzene and carbon tetrachloride (1 : 2). Compound 11 was recrystallized from petroleum ether.

Compound 19. The amount of carbon tetrachloride taken was 15 ml. After completion of the reaction, the solution was filtered hot, and after 2 hours the crystals which separated were filtered off with suction, washed with benzene, and recrystallized.

Compound 20 was sparingly soluble in carbon tetrachloride; therefore the reaction was carried out in 100 ml of benzene. The solution was filtered hot, the crystals separating on cooling were filtered off with suction, washed with benzene, and recrystallized.

Compound 21. In the presence of a solvent, 2,6-dichloro-4-nitroaniline reacted with phenyl tetrachlorophosphorane very slowly and incompletely; therefore, to prepare compound 21, a mixture of the initial substances was heated without a solvent initially at 110°, the temperature being gradually raised during 2 hours at 180°. To the cooled reaction mixture was added 150 ml of carbon tetrachloride, and the mixture was heated to boiling and filtered. The crystals which separated were filtered off with suction and recrystallized.

Hydrolysis of the phenyldichlorophosphazoyls. Salts of phenylphosphinic acid. The phenyldichlorophosphazoyl (0.2 g-mole) was added to 10-20 ml of water heated to 60-80°; a vigorous reaction took place. The mixture was heated to boiling, the solution was filtered hot from by-products and evaporated to dryness in vacuum. The sparingly



soluble phenylphosphinic acid salts of p-chloroaniline and p-bromoaniline separated as precipitates on cooling a solution. Thus, salts of phenylphosphinic acid were obtained.

Aniline salt; yield 70%, needles, m.p. 211-213° (from water).

Found %: N 5.86, 5.76. Equiv. 1.96, 2.00  $C_{12}H_{14}O_3NP$ . Calculated %: N 5.58. Equiv. 2.00.

p-Toluidine salt; yield 86%, m.p. 204-206°, needles (from a mixture of alcohol and ether).

Found equiv. 1.93, 1.90.  $C_{13}H_{16}O_3NP$ . Calculated equiv. 2.00.

p-Chloroaniline salt; yield 81%, darkens at 220°, plates (from water).

Found %: Cl 12.51, 12.48. Equiv. 1.96, 1.97.  $C_{12}H_{13}O_3NCIP$ . Calculated %: Cl 12.43. Equiv. 2.00.

p-Bromoaniline salt; yield 84%, darkens at 217°, plates (from water).

Found equiv. 1.95, 1.96.  $C_{12}H_{13}O_3NBrP$ . Calculated equiv. 2.00.

p-Anisidine salt; yield 70%, m.p. 200°, with darkening, needles (from water).

Found %: N 5.13, 5.22. Equiv. 1.98, 1.99.  $C_{13}H_{16}O_4NP$ . Calculated %: N 4.98. Equiv. 2.00.

All the salts were fairly soluble at room temperature in water and alcohol, readily soluble in hot water and alcohol, and insoluble in nonpolar solvents. The p-chloroaniline and p-bromoaniline salts were sparingly soluble in hot water.

#### SUMMARY

1. The action of phenyltetrachlorophosphorane on aromatic amines gives phenyldichlorophosphazoyls.
2. The phenyldichlorophosphazoyls obtained from aromatic amines of relatively high basicity ( $K_{base}$  of the order of  $10^{-9}$ – $1 \cdot 10^{-10}$ ) are dimeric in the solid state; all the others are monomeric. In solution, all the phenyldichlorophosphazoyls are monomeric.
3. Replacement of one chlorine atom in trichlorophosphazoyls by a phenyl group sharply diminishes the tendency to dimerization.
4. Phosphazo compounds of the type  $ArN=PX_3$  have a greater tendency to dimerization the smaller the electronegativity of Ar and the greater the electronegativity of the group X.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# INVESTIGATIONS IN THE ALLOXAZINE AND ISOALLOXAZINE SERIES

## V. CATALYSTS FOR THE REACTION OF SECONDARY AROMATIC ORTHOAMINOAZO COMPOUNDS WITH TRIHYDROXYPYRIMIDINES

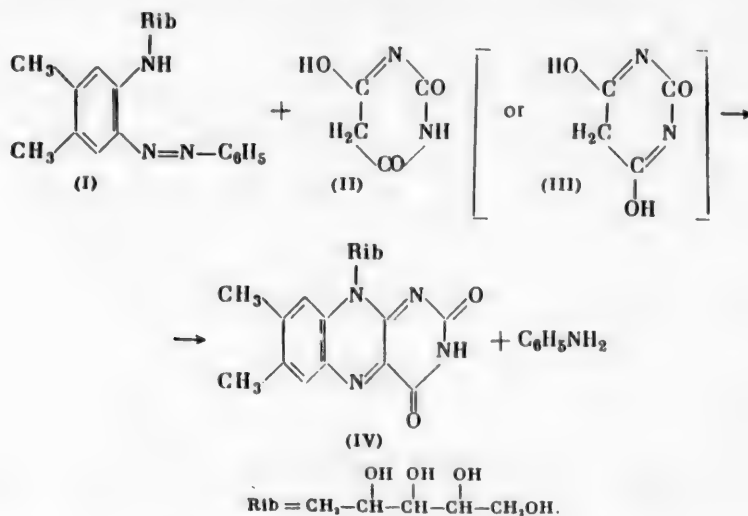
V. M. Berezovskii, L. S. Tul'chinskaya, T. A. Eremenko,  
E. P. Rodionova, and M. A. Barskaya

The All-Union Scientific Research Vitamin Institute  
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In the previous investigations of this series in our laboratory, methods for the synthesis of alloxazines by the condensation of aromatic o-diamines with alloxan [1] and of aromatic o-aminoazo compounds with trihydroxypyrimidines containing a labile hydrogen atom in position 5 have been studied [2-4]. The use of acetic acid as a catalyst for this reaction is known [5]. The present paper gives further information on our investigation of the formation of isoalloxazines by the cyclization of secondary aromatic o-aminoazo compounds with barbituric acid.

In the direct condensation of primary o-aminoazo compounds with barbituric acid ( $K = 9.8 \cdot 10^{-15}$ ), the latter reacts in the trioxo tautomeric form (V) and the yield of lumichrome, for example, is quite high, reaching 70% [2]. As we have shown, stronger acids, suppressing the enolization of the barbituric acid (in particular, oxalic acid) may be catalysts for this reaction [2].

In contrast to condensation with primary o-aminoazo compounds, the direct condensation of the secondary o-aminoazo compounds (I) with barbituric acid by boiling in n-butyl alcohol leads to riboflavin (IV) with a yield of 21%. The low yield of compound (IV) may be due to the insufficient degree of enolization of the barbituric acid which must react in the enolized form (II) or (III) in the production of isoalloxazines.



In the crystalline state, barbituric acid is present in the trioxo tautomeric form (V) [6] and not in the enolized form; this is shown by its IR absorption spectrum with intense bands characteristic for CO groups and no absorption in the regions corresponding to the hydroxyl group and to C=C and C=N bonds. In solution, barbituric acid is dissociated and, apparently, may exist in the mono-, di-, and trienolic forms [7].

The enolization of barbituric acid depends on the pH of the medium, which explains the different intensities of absorption (Fig. 1). In aqueous solution barbituric acid has pH 3.2 and  $\epsilon$  4400 at  $\lambda_{\max}$  256 m $\mu$ . However, a greater intensity of absorption is observed in the pH range from 5 to 10: At pH 5.2,  $\epsilon$  is 18800, and at pH 7.0  $\epsilon$  is 19700; apparently the intensity is connected with the presence of an  $\alpha,\beta$ -unsaturated carbonyl system with a hydroxyl group at the end (tautomeric form VI), which, as is well known, is characterized by a high extinction. It may be assumed that under these conditions barbituric acid exists exclusively in the mono-enolic form with one double bond in the ring.

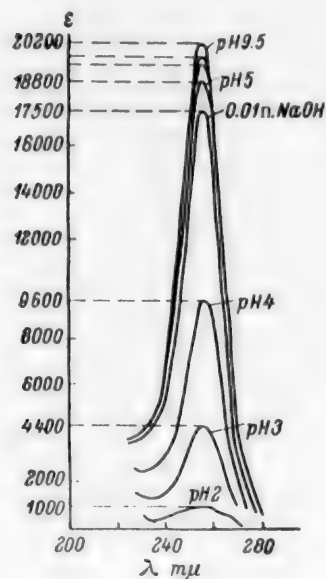
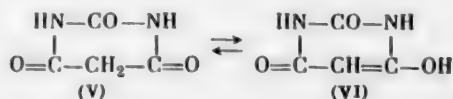
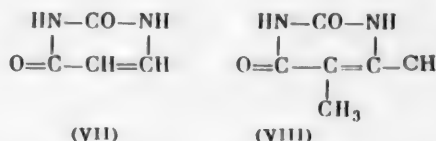


Fig. 1. IR spectrum of barbituric acid (in water).



The intensity of absorption of barbituric acid in buffer solutions at the same pH's is somewhat higher [8].

It is characteristic that intense absorption (although less than for barbituric acid) is observed for uracyl (VII) ( $\lambda_{\max}$  260 m $\mu$ ,  $\epsilon$  9000) [9] and thymine (VIII) ( $\lambda_{\max}$  262 m $\mu$ ,  $\epsilon$  8700 [8],  $\alpha,\beta$ -unsaturated carbonyl systems of which are fixed; the smaller value of the absorption for these compounds is apparently connected with the absence of a hydroxyl group at the end of the conjugated system.



As one passes from an acid medium to a neutral medium, in addition to the tautomeric form of barbituric acid with the  $\alpha,\beta$ -unsaturated carbonyl system determining the position of the maximum and the greatest intensity of the absorption, it is probable that a lactam-lactim tautomeric system conjugated with the carbonyl group, for example, in a form corresponding to form (II) arises, and then also the dienolic cumulated form (III), which contains a methylene group and two lactim groups; these two forms may be considered the most active in reactions with secondary o-aminoazo compounds.

At lower values of the pH, barbituric acid exhibits only a low absorption—at pH 2.2,  $\epsilon$  is 1000. The sharp decrease in the intensity of absorption of barbituric acid in an acid medium may be explained by the pronounced diminution in the degree of dissociation, which, with an increasing concentration of  $\text{H}^+$  ions, approaches zero.

Thus, it may be assumed that weaker acids, ensuring the enolization of the barbituric acid, will be catalysts for the condensation of barbituric acid with secondary o-aminoazo compounds. In fact, we have found several catalysts for the reaction among the weak organic acids with  $K$  from  $1.2 \cdot 10^{-5}$  to  $6.89 \cdot 10^{-5}$ : These include benzoic, p-amino-benzoic, phenylacetic, nicotinic, and succinic acids. The yield of riboflavin with these catalysts amounts to 65-70%.

Organic acids with dissociation constants greater than, but quite close to, that of barbituric acid (formic, p-nitrobenzoic, citric, malonic, monochloroacetic, etc.;  $K$  from  $1.76 \cdot 10^{-4}$  to  $1.50 \cdot 10^{-3}$ ) are weaker catalysts for the reaction. The yields of riboflavin amount to 32-55% (see table).

In addition to riboflavin, we isolated from the reaction mixture a by-product—*aniline*—formed as a result of a cyclization taking place through the reaction of the active hydrogen atoms of the methylene group of barbituric acid with the azo group of compound (I) and the reaction of the secondary amino group of this compound with a hydroxyl group of the tautomeric form of barbituric acid; the reaction is accompanied by the splitting out of water.

We studied the kinetics of the condensation of 3,4-dimethylphenyl-6-phenylazo-N-D-ribitylamine (I) with barbituric acid in riboflavin with the catalytic participation of acetic acid. The optimum length of the reaction at 68.3° in the reaction medium is 42-48 hours; at 82.5°, 15-18 hours; and at 100°, about 8 hours. Thus increasing the temperature from 68.3 to 82.5° (by 14.2°) accelerates the reaction 2.5-3 times, and from 82.5 to 100° (by 17.5°), 2 times (Fig. 2).

Name of the acid	$K \cdot 10^5$	Yield of riboflavin (in %)
p-Aminobenzoic . . . . .	1.20	65
Nicotinic . . . . .	1.40	62
Acetic . . . . .	1.76	69
Phenylacetic . . . . .	4.88	70
Benzoic . . . . .	6.27	70
Succinic . . . . .	6.65	65
Formic . . . . .	21.4	49
p-Nitrobenzoic . . . . .	37.6	55
Citric . . . . .	84.0	44
Monochloroacetic . . . . .	140	32
Malonic . . . . .	149	40

The influence of an excess of barbituric acid on the yield of riboflavin was studied in a series of experiments. It was found that the optimum yield of riboflavin (69%) is associated with the use of barbituric acid in an amount of 1.6-2 g-mole per 1 g-mole of the azo compound (I). If 1 g-mole of barbituric acid per 1 g-mole of 3,4-dimethylphenyl-6-phenylazo-N-D-ribitylamine (I) is used, the yield falls to 61.1%, i.e., by 12.6% (Fig. 3, curve 2). The presence of water in the reaction mixture also leads to a diminution in the yield of riboflavin; thus, for example, with 81% aqueous alcohol the yield of riboflavin is only 60.6% (Fig. 3, curve 1).

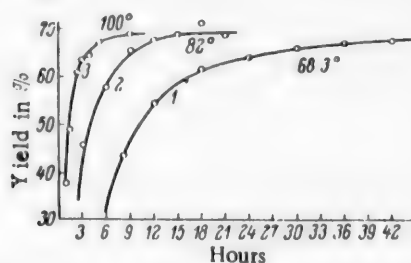


Fig. 2. Influence of the temperature and time of reaction on the yield of riboflavin.

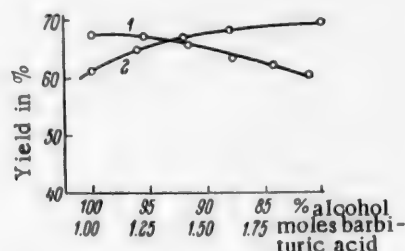


Fig. 3. Influence of the amount of water in the reaction medium (1) and the excess of barbituric acid (2) on the yield of riboflavin.

Starting from the assumption that the aniline formed as a result of reductive cyclization may give a salt with the barbituric acid and thereby remove it from the reaction sphere (the necessity for a large excess of it possibly being a consequence of this), condensation using the aniline salt of barbituric acid was investigated. It was found that under these conditions the reaction proceeds in the usual way and riboflavin is obtained with the same optimum yield (70%); apparently, this salt readily dissociates during the reaction.

Using the same method of synthesis—the condensation of barbituric acid with the appropriate azoglucamines possessing an unsubstituted ortho position with respect to the azo group, we obtained stereoisomers of riboflavin: D-araboflavin and D-xyloflavin; these flavins have previously been obtained by the condensation of substituted ortho-diamines with alloxan [10, 11].

#### EXPERIMENTAL PART

**Riboflavin.** 6,7-dimethyl-9-(D-ribit-1-yl)-isoalloxazine (IV). The experiments with different catalysts in the study of the kinetics and the influence of various factors on the yield were carried out according to the following typical description. A mixture of 3 g of 3,4-dimethylphenyl-6-phenylazo-N-D-ribitylamine (I) with m.p. 174-175°, 1.8 g of barbituric acid, 4.2 g of the organic acid, and 21 ml of alcohol (butyl, ethyl, or methyl) was boiled with stirring. In the experiments in which the influence of an excess of barbituric acid was studied, it was used in an amount of from

1 to 2 g-mole. As the reaction proceeded, the azo compound and the barbituric acid passed into solution, and a dark yellow precipitate gradually separated from it. After the completion of the reaction, the mixture was cooled, and the precipitate was filtered off and washed with 5 ml of alcohol and 10 ml of boiling water. The dry substance was dissolved in 10 ml of 24% hydrochloric acid and a few drops of hydrogen peroxide were added to the solution; this was filtered from a small amount of precipitate and the filtrate was poured into 80 ml of water heated to 75-80°. On the following day, the precipitate was filtered off, washed with water, and dried. The riboflavin was obtained in the form of orange-yellow needles with m.p. 282° (decomp.); it was analysed by the fluorometric method.

**Isolation of aniline.** The mother liquor, after the removal of the riboflavin, was acidified with sulfuric acid (to Congo red), the solvent was distilled off, the residue was basified with caustic soda solution to pH 8-9, and the aniline was distilled off with steam. The materials from the aqueous distillate and the oil were taken up in ether and the solvent was distilled off. A yield of 0.35 g of aniline (a sample gave an intense blue-violet coloration with bleaching powder) was obtained. It was treated with 1.3 ml of acetic anhydride and yielded acetanilide with m.p. 113-114°; the substance gave no depression of the melting point when mixed with a known sample.

**Catalysts for the reaction.** The experiments were carried out with various organic acids in n-butyl alcohol for 5 hours (see table).

**Kinetics of the reaction.** The kinetics of the condensation was studied in three series of experiments. In the first series, acetic acid and methyl alcohol were used; b.p. 66.8° in the vapors and 68.3° in the reaction mixture; reaction time from 6 to 42 hours. In the second series, acetic acid and 96% ethyl alcohol were used; b.p. 79.5° in the vapors and 82.5° in the reaction mixture; reaction time from 3 to 21 hours. In the third series, acetic acid and 96% ethyl alcohol were used; the reaction was carried out in sealed tubes at a temperature of the reaction mixture of 100° (Fig. 2).

**Influence of excess of barbituric acid.** A series of experiments was carried out with acetic acid and 96% ethyl alcohol during 15 hours; the excess above the theoretical amount varied from 0 to 100% (Fig. 3).

**Influence of water in the reaction mixture on the yield of riboflavin.** A series of experiments was carried out with acetic acid and ethyl alcohol with a concentration from 81 to 100%; the reaction time was 15 hours (Fig. 3).

**Use of the aniline salt of barbituric acid in the condensation reaction.** Instead of barbituric acid, an equivalent amount of its aniline salt was used; the reaction was carried out in acetic acid in 96% ethyl alcohol for 15 hours. A yield of 2.2 g (70%) of riboflavin was obtained.

**Aniline salt of barbituric acid.** A mixture of 1 g of barbituric acid, 2.5 g of aniline, 100 ml of ethyl alcohol, and 0.6 ml of glacial acetic acid was heated at the boil for 5 hours. Then the reaction solution was filtered in the hot, and the residue was washed with 10 ml alcohol and dried. After recrystallization, from water, the colorless aniline salt of barbituric acid was obtained. The content of the salt was determined in 1% aqueous solution by titration with 0.1 N NaOH in the presence of phenolphthalein.

Found %: Barbituric acid 57.40, 57.70.  $C_4H_4O_3N_2 \cdot C_6H_7N$ . Calculated %: Barbituric acid 57.90.

The salt gives the qualitative reaction for violuric acid with sodium nitrite in the presence of alkali (formation of an intense violet color).

**D-Arabo flavin.** This was obtained from 3,4-dimethylphenyl-6-phenylazo-N-D-arabitylamine [12] and barbituric acid in the presence of acetic acid in dioxane in the same way as riboflavin; the substance was isolated in the form of orange-yellow needles with an absorption spectrum (in water) identical in respect of the magnitude of the extinction and the position of the absorption maxima ( $\lambda_{\max}$  223, 266, 372, 445 m $\mu$ ) with that of riboflavin.

**D-Xylo flavin.** This was obtained from 3,4-dimethylphenyl-6-phenylazo-N-D-xylylamine [12] under the conditions described above; it formed orange-yellow needles with an absorption spectrum identical with that of riboflavin.

## SUMMARY

1. It has been shown that weak organic acids with K from  $1.2 \cdot 10^{-5}$  to  $1.5 \cdot 10^{-3}$  are catalysts for the cyclization reaction of 3,4-dimethylphenyl-6-phenylazo-N-D-ribitylamine with barbituric acid to form riboflavin; of these the best are: Acetic, benzoic, phenylacetic, p-aminobenzoic, and succinic acids.

2. The influence of various factors on the yield of riboflavin has been studied: Temperature, excess of reactants, moisture, and the amount of catalyst.
3. Considerations on the tautomeric conversions of barbituric acid have been expressed.
4. D-arboflavin and D-xyloflavin have been obtained by the cyclization of barbituric acid with the corresponding aromatic orthoazoglutamines.

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## $\beta$ -DICARBONYL COMPOUNDS

### XII. PERFORMANCE OF NUCLEOPHILIC REACTIONS OF DIHYDRORESORCINOL AND ITS DERIVATIVES IN SOLVENTS OF LOW POLARITY

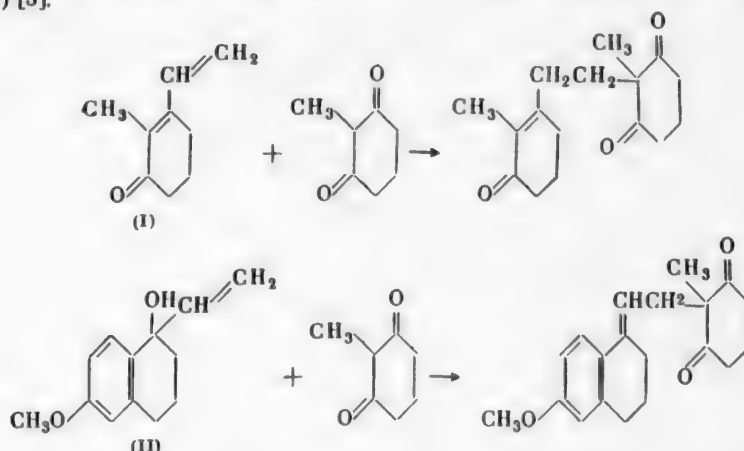
S. I. Zav'yalov, G. V. Kondrat'eva, and L. F. Kudryavtseva

The N. D. Zelinskii Institute of Organic Chemistry  
of the Academy of Sciences of the USSR

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 11,  
pp. 3695-3700, November, 1961

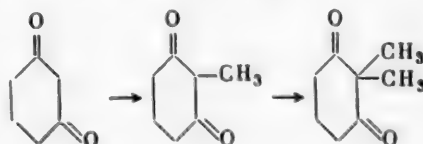
Original article submitted December 14, 1960

The nucleophilic reactions of dihydroresorcinol and its derivatives are generally carried out in highly polar solvents (alcohol, aqueous dioxane, aqueous acetone) [1]. However, in some cases the use of aromatic hydrocarbons as solvents gives good results, for example, in the condensation of 2-methyldihydroresorcinol with the dienone (I) [2] and with vinyl alcohol (II) [3].



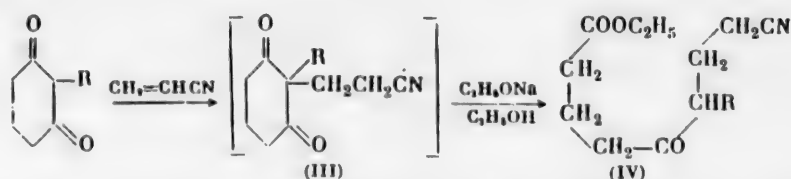
In view of this, it was of interest to carry out a more detailed study, with typical examples, of the influence of solvents of low polarity on the course of the nucleophilic reactions of dihydroresorcinol and its derivatives.

As was to be expected, methylation of the sodium derivative of dihydroresorcinol takes place in benzene more slowly than in polar solvents, and only after 25 hours' boiling can a mixture of 2-methyl- and 2,2-dimethyl-dihydroresorcinols be isolated with yields of 26 and 14%, respectively.

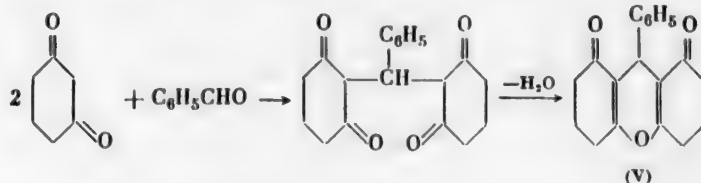


In aqueous acetone, the same reaction takes place in 2-3 hours with yields of 2-methyl- and 2,2-dimethyldihydroresorcinols of 42 and 15% [4]. The sodium and pyridine salts of dihydroresorcinol and dimedone do not react with acrylonitrile even when the reactants are heated in boiling benzene or toluene for 4-5 hours. The best solvent for the cyanoethylation of cyclic  $\beta$ -diketones is aqueous dioxane [5]. Alcohol is not suitable for the preparation of 2-alkyl-

2-cyanoethyldihydroresorcinols (III), since this solvent causes the alcoholysis of the reaction products with the formation of ketoesters (IV) [6].

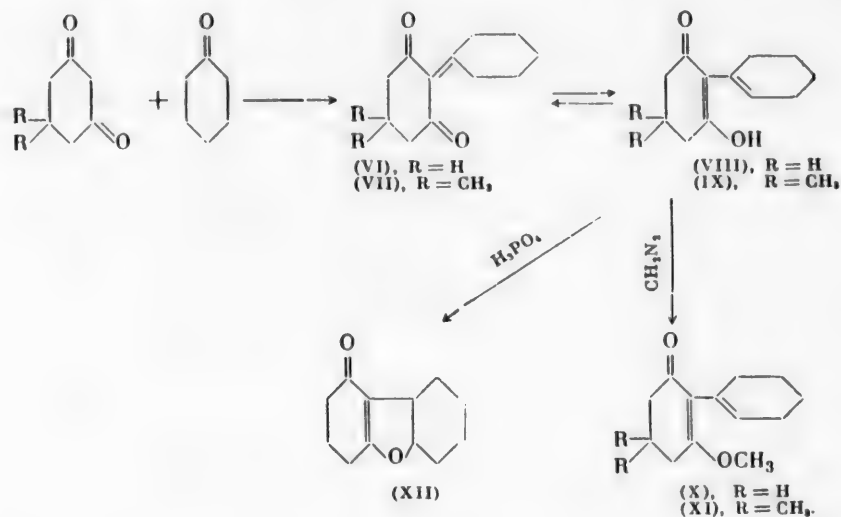


In boiling toluene, in the presence of *p*-toluenesulfonic acid, dihydroresorcinol reacts smoothly with benzaldehyde giving the anhydro derivative of benzylidene-bis-dihydroresorcinol.

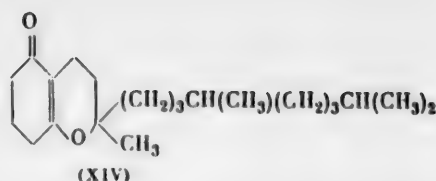
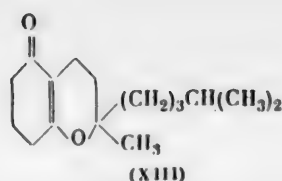


Under the usual conditions (methanol or ethanol, piperidine as catalyst), with aldehydes dihydroresorcinol forms alkylidene- (or arylidene-) bis-dihydroresorcinols, which are cyclized into the anhydro derivatives of the type of (V) under the action of water-removing agents, for example acetic anhydride [7].

In spite of literature data [8], we showed (with cyclohexanone as an example) that dihydroresorcinol and dimedone are capable of taking part in the crotonic condensation with ketones. The reaction is carried out in boiling xylene or toluene in the presence of pyridine and leads to the corresponding condensation products (VI, VII or VIII, IX) which proved to be extremely unstable and were therefore not isolated in analytically pure form.



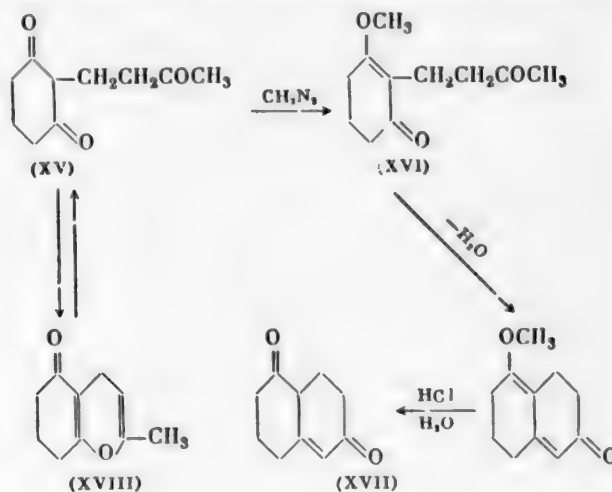
The action of diazomethane in ethereal solution on the freshly-prepared condensation products leads to the formation of the stable methyl ethers (X) and (XI). These enol ethers and keto-enols (VI or VIII) and (VII or IX) possess almost identical values for the maxima in the ultraviolet region, which indicates the presence of the enolic forms (VIII) and (IX), probably present in tautomeric equilibrium with the diketone forms (VI) and (VII). On heating with phosphoric acid, the keto-enol (VIII) gives 1-oxo-1,2,3,4,5a,6,7,8,9,9a-decahydrodibenzofuran (XII), the structure of which is confirmed by the presence of a maximum at 405  $\text{m}\mu$  for the corresponding 2,4-dinitrophenylhydrazone, which is characteristic for the 2,4-dinitrophenylhydrazones of internal enol ethers of dihydroresorcinol, for example (XIII) and (XIV). The absorption maxima of the 2,4-dinitrophenylhydrazones of these compounds are at 406 and 401  $\text{m}\mu$ , respectively.



Dihydroresorcinol and dimedone do not take part in the crotonic condensation with cyclohexanone in aqueous solution (pyridine, 100°, 4 hours), probably in consequence of the displacement of the equilibrium in the direction of the initial components.



Probably for the same reason, Vorländer [8] did not succeed in bringing dimedone into reaction with ketones in aqueous alcohol. Under the usual conditions, in the presence of alkaline catalysts, 2-(γ-oxybutyl)-dihydroresorcinol (XV) does not undergo an intramolecular crotonic condensation [9]. To obtain the diketone (XVII), recourse must be had to a roundabout route including the stage of the cyclization of the methyl ester (XVI) [10].



On heating 2-(γ-oxybutyl)-dihydroresorcinol (XV) in boiling toluene in the presence of p-toluenesulfonic acid, it cyclizes to form 2-methyl-5-oxo-5,6,7,8-tetrahydro-1,4-benzopyran (XVIII), which was obtained earlier by boiling the triketone (XV) with acetic anhydride [11].

The benzopyran (XVIII) is very sensitive to the action of water and is readily hydrolyzed, particularly in the presence of acid, to the initial triketone XV).

#### EXPERIMENTAL PART

**Methylation of dihydroresorcinol.** To a solution of the alkoxide prepared from 1.2 g of metallic sodium and 20 ml of methanol, 5.6 g of dihydroresorcinol was added, and the solution obtained was evaporated in vacuum to dryness. The residue was stirred with 25 ml of benzene and 11 g of methyl iodide and boiled for 25 hours. The precipitate was filtered off, washed with water, and recrystallized from aqueous alcohol. A yield of 1.6 g (26%) of 2-methyldihydroresorcinol with m.p. 204-205° [4] was obtained. The benzene mother liquors yielded 1.1 g (14%) of 2,2-dimethyldihydroresorcinol with b.p. 72-73° at 3 mm and m.p. 39-40° [4].

Reaction of dihydroresorcinol with benzaldehyde. A mixture of 5.6 g of dihydroresorcinol, 5.6 g of benzaldehyde, 0.3 g of *p*-toluenesulfonic acid, and 30 ml of toluene was boiled for 20 minutes. The precipitate which separated was filtered off and washed with water. A yield of 6 g (80%) of the anhydro derivative (V) of benzyldiene-bis-dihydroresorcinol was obtained, with m.p. 252-254°, giving no depression of the melting point in admixture with a known sample, (m.p. 255°) prepared by the cyclization of benzyldiene-bis-dihydroresorcinol [7].

Condensation of dihydroresorcinol with cyclohexanone. A mixture of 5.6 g of dihydroresorcinol, 7.5 g of cyclohexanone, 7.5 g of pyridine, and 40 ml of toluene was boiled with a water-separator for 4 hours. The cooled solution was washed with dilute hydrochloric acid and then with 10% caustic soda (two 30 ml portions). On acidifying the alkaline solution with hydrochloric acid, 5 g of the condensation product, having structure (VI) or (VIII) with m.p. 109-118° separated;  $\lambda_{\max}$  264 m $\mu$  (alcohol). This substance proved to be extremely unstable and was therefore converted into the methyl ester (X) without further purification, using diazomethane in ethereal solution. A yield of 0.7 g of the methyl ester (X) with m.p. 102-104°, isolated by freezing out from ether with solid carbon dioxide, was obtained from 2.5 g of the condensation product. After recrystallization from a mixture of heptane and benzene, it had m.p. 105-106°,  $\lambda_{\max}$  267 m $\mu$  (log  $\epsilon$  4.098) (alcohol).

Found %: C 75.84, 75.90; H 8.87, 8.79.  $C_{13}H_{18}O_2$ . Calculated %: C 75.88; H 8.79.

Reaction of dimedone with cyclohexanone. A mixture of 7 g of dimedone, 7.5 g of cyclohexanone, 7.5 g of pyridine, and 40 ml of toluene was boiled with a water-separator for 3 hours. On washing the cooled solution with dilute hydrochloric acid, 6.2 g of the condensation product with the structure (VII or IX) separated, with m.p. 92-95°. After recrystallization from toluene, it had m.p. 95-115°,  $\lambda_{\max}$  270 m $\mu$  (in alcohol).

Found %: C 75.75, 75.50, H 9.07, 9.02.  $C_{14}H_{20}O_2$ . Calculated %: C 76.32, H 9.15.

This substance is extremely unstable and rapidly changes on storage. By the action of diazomethane in ethereal solution, 3 g of the freshly-prepared unrecrystallized condensation product with m.p. 92-95° yielded 2 g of the methyl ether (XI) with m.p. 66-69° (freezing out from ethereal solution with solid carbon dioxide). After recrystallization from a mixture of benzene and heptane, it had m.p. 76-77°,  $\lambda_{\max}$  269 m $\mu$  (log  $\epsilon$  4.036) (alcohol).

Found %: C 76.69, 76.79; H 9.47, 9.32.  $C_{15}H_{22}O_2$ . Calculated %: C 76.68, H 9.46.

Conversion of the condensation product (VIII) into 1-oxo-1,2,3,4,5a,6,7,8,9,9a-decahydrodibenzofuran (XII). A mixture of 4.5 g of the condensation product (VIII) and 20 ml of 80% phosphoric acid was heated for 4 hours at 100°. The reaction mixture was diluted with 200 ml of water and, after neutralization with sodium carbonate, the cyclization product was extracted with ether. A yield of 2.3 g (51%) of 1-oxo-1,2,3,4,5a,6,7,8,9,9a-decahydrodibenzofuran (XII) was obtained, with b.p. 116-118° at 2 mm,  $n_D^{19}$  1.5415.

Found %: C 74.79, 74.90; H 8.55, 8.32.  $C_{12}H_{16}O_2$ . Calculated %: 75.00; H 8.39.

2,4-Dinitrophenylhydrazone: M.p. 206-207° (from alcohol),  $\lambda_{\max}$  405 m $\mu$  (alcohol).

Found %: N 14.65, 14.79.  $C_{18}H_{20}O_5N_4$ . Calculated %: N 15.05.

Cyclization of 2-( $\gamma$ -oxobutyl)-dihydroresorcinol. A mixture of 4 g of 2-( $\gamma$ -oxobutyl)-dihydroresorcinol (m.p. 104-106° [10]), 0.4 g of *p*-toluenesulfonic acid, and 20 ml of toluene was boiled with a water-separator for 1 hour. The cooled solution was washed with dilute alkali and dried with magnesium sulfate, and, after removal of the solvent, the residue was distilled. A yield of 1.4 g (39%) of the cyclization product (XVIII) was obtained, with b.p. 95-96° at 2 mm and m.p. 40-42° (from ether). The substance gave no depression of the melting point in admixture with a known sample of 2-methyl-5-oxo-5,6,7,8-tetrahydro-1,4-benzopyran prepared by boiling 2-( $\gamma$ -oxobutyl)-dihydroresorcinol (XV) with acetic anhydride. The action of dilute hydrochloric acid (1:1) (12 hours, 20°) converted the cyclization product (XVIII) into 2- $\gamma$ -oxobutyl-dihydroresorcinol (XV) almost quantitatively.

#### SUMMARY

1. The nucleophilic reactions of dihydroresorcinol and its derivatives in such low-polarity solvents as benzene, toluene, and xylene have been investigated.
2. On heating the sodium derivative of dihydroresorcinol with methyl iodide in boiling benzene for 25 hours, a mixture of 2-methyl- and 2,2-dimethyl-dihydroresorcinols is formed with yields of 26 and 14%, respectively.

3. By the action of benzaldehyde in boiling toluene in the presence of p-toluenesulfonic acid, dihydroresorcinol forms the anhydro derivative (V) of benzylidene-bis-dihydroresorcinol.

4. Dihydroresorcinol and dimedone take part in the crotonic condensation with cyclohexanone under the influence of pyridine in boiling xylene or toluene.

5. In boiling toluene in the presence of p-toluenesulfonic acid, 2-( $\gamma$ -oxobutyl)-dihydroresorcinol (XV) undergoes cyclization with the formation of 2-methyl-5-oxo-5,6,7,8-tetrahydro-1,4-benzopyran (XVIII).

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## INVESTIGATION OF PYRAZOLES

### XXII. THE CYANOETHYLATION OF PYRAZOLES

I. I. Grandberg and A. N. Kost

The M. V. Lomonosov Moscow State University

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The ability of pyrazoles readily to add substances with an active double bond at the NH group [1] is of considerable interest from the point of view of using this reaction for protecting the NH group. In view of this, we have undertaken the study of the cyanoethylation reaction of pyrazoles and the search for methods of removing the cyanoethyl "protection" having in view the performance of a series of reactions which proceed only with pyrazoles substituted on the nitrogen atom of the ring [2, 3].

It was found that pyrazoles smoothly add acrylonitrile in the presence of both acidic and alkaline catalysts. However, the optimum conditions are the absence of catalysts, a small excess of acrylonitrile, a reaction temperature of 140-160°, and a time of 4-5 hours.

In not one case did we succeed in carrying out the cyanoethylation of 4-iodopyrazoles; under mild conditions no reaction took place, while under severe conditions complete resinification set in. At the same time, 4-chloro- and 4-bromopyrazoles cyanoethylated normally.

Attempts to carry out cyanoethylation at the carbon atom in position 4 of the ring were unsuccessful, even though sodium ethoxide, caustic soda, aluminum chloride and bromide, stannic chloride, and boron trifluoride were used as catalysts. The reaction did not take place even under the severe conditions of the  $\beta$ -cyanoethylation of indole [4].

On investigating the lability of a cyanoethyl group on the nitrogen atom of the pyrazole ring, it was found that acid and alkaline media are not capable of splitting off acrylonitrile and complicate the reaction by the partial formation of an acid through hydrolysis. Attempts to carry out the reaction of decyanoethylation were also unsuccessful.

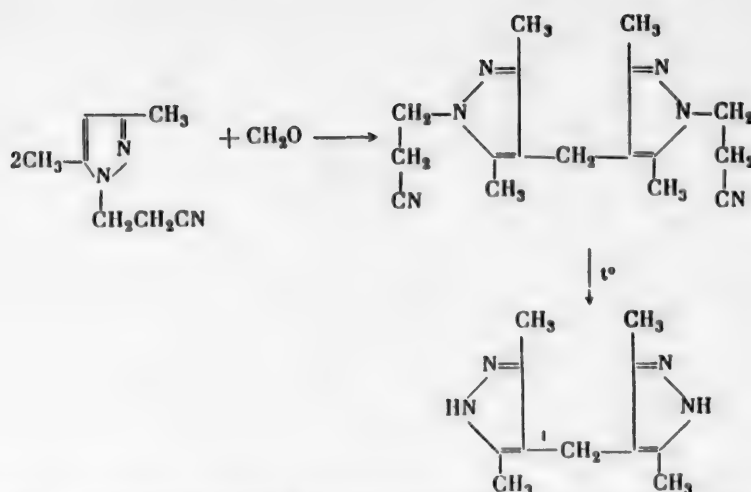
The optimum conditions for removing the cyanoethyl group were slow thermal decomposition, acrylonitrile being distilled off.

The lability of the cyanoethyl group changes considerably according to the structure of the initial pyrazole. 3,5-Dimethyl-1-(2'-cyanoethyl)-pyrazole which exhibits considerable basic properties, split out the cyanoethyl "protection", even at 180-200°. 3,5-Diphenyl-1-(2'-cyanoethyl)-pyrazole, the basicity of which is considerably less, split out the cyanoethyl group only at 270-300°.

4-Halogeno-1-(2'-cyanoethyl)-pyrazoles which exhibit almost no basic properties did not split out the cyanoethyl group under mild conditions and resinified completely in attempts to remove the cyanoethyl group under severe conditions (above 300°).

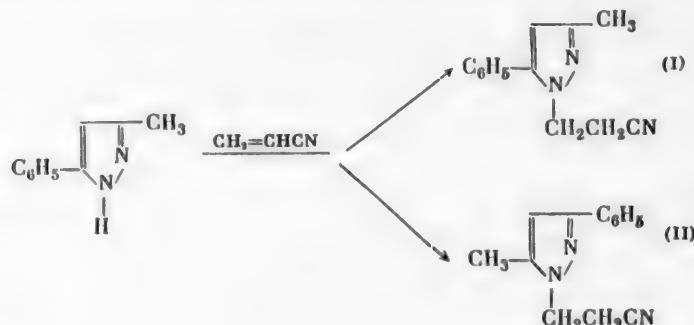
We successfully used the method of cyanoethyl "protection" for linking two pyrazole rings by a methylene bridge in position 4 of the two rings.





We were previously [3] unable to carry out this reaction with pyrazoles having a free NH group.

On cyanoethylating 3(5)-methyl-5(3)-phenylpyrazole, we obtained a mixture of two substances (I) and (II) in a ratio of ~30:1.



On the basis of literature data indicating that alkylation of 3(5)-methyl-5(3)-phenylpyrazole leads mainly to 1-alkyl-3-methyl-5-phenylpyrazoles [5], we consider that the main product of cyanoethylation is 1-(2'-cyanoethyl)-3-methyl-5-phenylpyrazole (I).

The nitrile group in the cyanoethylated pyrazoles is smoothly reduced to an amino group by hydrogenation over skeletal nickel (100 atm.,  $120^\circ$ ). Under these conditions we observed no hydrogenation of the pyrazole ring.

#### EXPERIMENTAL PART\*

**3,5-Dimethyl-1-(2'-cyanoethyl)-pyrazole.** A mixture of 9.6 g of 3,5-dimethylpyrazole and 5.9 g of freshly-distilled acrylonitrile was heated in a sealed tube at  $130^\circ$  for 4 hours. On distilling the reaction mixture, 13.1 g (87%) of 3,5-dimethyl-1-(2'-cyanoethyl)-pyrazole was obtained, with b.p.  $121-123^\circ$  (4 mm), m.p.  $48^\circ$  (from heptane).

Picrate, m.p.  $159^\circ$  (from alcohol) [1].

On carrying out the reaction in an open vessel, the mixture being boiled without a catalyst ( $70-120^\circ$ , 5 hours), the yield was 74%. In the presence of catalytic amounts of sodium alkoxide (0.5 hours), the yield was 70%. In the presence of traces of acetic acid (1 hour), the yield was 59%.

**3,5-Diphenyl-1-(2'-cyanoethyl)-pyrazole.** A mixture of 19.6 g of 3,5-diphenylpyrazole [6] and 6 g of freshly-distilled acrylonitrile was heated in a sealed tube at  $150^\circ$  for 4 hours. The reaction mass was dissolved in 40 ml of

\* With the participation of A. V. Potapova.

benzene and filtered from the polymer. The filtrate was diluted with 50 ml of petroleum ether and the 3,5-diphenyl-1-(2'-cyanoethyl)-pyrazole which separated was filtered off with suction. The yield was 18.5 (85%); m.p. 94-95° (from a mixture of benzene and petroleum ether).

Found %: N 14.98, 14.93.  $C_{18}H_{15}N_3$ . Calculated %: N 15.36.

Picrate, m.p. 117-117.5° (from methanol).

Found %: N 16.47, 16.40.  $C_{18}H_{15}N_3 \cdot C_6H_5O_7N_3$ . Calculated %: N 16.73.

3,5-Dimethyl-4-bromo-1-(2'-cyanoethyl)-pyrazole. This was obtained in a similar manner from 0.1 mole of 3,5-dimethyl-4-bromopyrazole [7], with a yield of 55%, m.p. 98° (from benzene).

Found %: C 41.98, 41.87; H 4.52, 4.30.  $C_8H_{10}N_3Br$ . Calculated %: C 41.94; H 4.40.

Picrate, m.p. 94-94.5° (from methanol).

Found %: N 18.23, 18.11.  $C_8H_{10}N_3Br \cdot C_6H_5O_7N_3$ . Calculated %: N 18.37.

3,5-Dimethyl-4-nitro-1-(2'-cyanoethyl)-pyrazole. This was obtained similarly from 0.1 g-mole of 3,5-dimethyl-4-nitropyrzole [7], with a yield of 48%, m.p. 71-72°.

Found %: C 49.54, 49.43; H 5.41, 5.36.  $C_8H_{10}O_2N_4$ . Calculated %: C 49.48; H 5.19.

Picrate, m.p. 72-73° (from methanol).

Found %: N 23.40, 23.37.  $C_8H_{10}O_2N_4 \cdot C_6H_5O_7N_3$ . Calculated %: N 23.16.

3,5-Dimethyl-4-chloro-1-(2'-cyanoethyl)-pyrazole. This was obtained similarly from 0.1 g-mole of 3,5-dimethyl-4-chloropyrazole [8], with a yield of 71%. M.p. 99.5-100° (from a mixture of benzene and petroleum ether).

Found %: C 52.63, 52.52; H 5.79, 5.66.  $C_8H_{10}N_3Cl$ . Calculated %: C 52.33; H 5.49.

Picrate, m.p. 98-99° (from methanol).

Found %: N 20.41, 20.31.  $C_8H_{10}N_3Cl \cdot C_6H_5O_7N_3$ . Calculated %: N 20.36.

3,5-Diphenyl-4-bromo-1-(2'-cyanoethyl)-pyrazole. This was obtained in a similar manner from 0.1 g-mole of 3,5-diphenyl-bromopyrazole, with a yield of 41%, m.p. 115-116° (from benzene).

Found %: N 13.28, 12.99.  $C_{18}H_{14}N_3Br$ . Calculated %: N 11.94.

Picrate, m.p. 102-103° (from methanol).

Found %: N 14.12, 14.07.  $C_{18}H_{14}N_3Br \cdot C_6H_5O_7N_3$ . Calculated %: N 14.48.

3,5-Diphenyl-4-chloro-1-(2'-cyanoethyl)-pyrazole. This was obtained in a similar manner from 0.1 mole of 3,5-diphenyl-4-chloropyrazole, with a yield of 69%, m.p. 86.5-88° (from benzene).

Found %: N 13.97, 13.88.  $C_{18}H_{14}N_3Cl$ . Calculated %: N 13.64.

Picrate, m.p. 113-114° (from methanol).

Found %: N 15.42, 15.38.  $C_{18}H_{14}N_3Cl \cdot C_6H_5O_7N_3$ . Calculated %: N 15.66.

Removal of the cyanoethyl group. 3,5-Dimethyl-1-(2'-cyanoethyl)-pyrazole (29.8 g) was heated to gentle boiling in a 50 ml Claisen flask with a 200 mm long fractionating column provided with a glass jacket. After 1.5 hours, 8.0 g of acrylonitrile had distilled off, and then 18 g (93.2%) of 3,5-dimethyl-pyrazole with b.p. 197-203°, m.p. 105-107° (from benzene) was isolated by distillation.

The cyanoethyl group of 3,5-diphenyl-1-(2'-cyanoethyl)-pyrazole was removed in a similar manner with a yield of 63% (at a temperature in the mixture of about 250-300°).

However, the presence of a chlorine or bromine atom or a nitro group in position 4 of the ring complicates the reaction and no pyrazoles with free NH groups could be isolated.

Bromination of 3,5-dimethyl-1-(2'-cyanoethyl)-pyrazole. A solution of 12 g of bromine in 10 ml of acetic acid was added slowly in drops to a suspension of 22.4 g of 3,5-dimethyl-1-(2'-cyanoethyl)-pyrazole and 12.3 g of

sodium acetate in 90 ml of water. The crystals separating out were removed. The yield was 16 g (47%) of a substance with m.p. 97° (from a mixture of benzene and petroleum ether). It gave no depression of the melting point in admixture with the 3,5-dimethyl-4-bromo-1-(2'-cyanoethyl)-pyrazole synthesized above. Under similar conditions, the iodination of 3,5-dimethyl-1-(2'-cyanoethyl)-pyrazole with a mixture of iodine and potassium iodide did not take place even at 100°.

Di-[3,5-dimethyl-1-(2'-cyanoethyl)-pyrazol-4'-yl]-methane. To a solution of 29.8 g of 3,5-dimethyl-1-(2'-cyanoethyl)-pyrazole in 20 ml of absolute dioxane was added 3.6 g of finely-ground paraformaldehyde, and the mixture was saturated with dry hydrogen chloride for 1 minute. The reaction mass was placed in an autoclave and heated at 150° for 4 hours. The reaction mass was transferred into a beaker, 100 ml of benzene was added, and the mixture was shaken with 100 ml of saturated sodium carbonate solution. The benzene extract was evaporated to a volume of 50 ml. After cooling, crystals di-[3,5-dimethyl-1-(2'-cyanoethyl)-pyrazol-4'-yl]-methane separated. The yield was 8 g (26%); m.p. 159-161° (from methanol). The IR spectrum showed the absence of NH group in the 3000-3500  $\text{cm}^{-1}$  region.

Found %: C 65.85, 65.72; H 7.13, 6.98.  $\text{C}_{17}\text{H}_{22}\text{N}_6$ . Calculated %: C 65.78; H 7.14.

Picrate, m.p. 154-156° (from methanol).

Found %: N 21.41, 21.34.  $\text{C}_{17}\text{H}_{22}\text{N}_6 \cdot 2\text{C}_6\text{H}_3\text{O}_7\text{N}_3$ . Calculated %: N 21.86.

Di-(3,5-dimethylpyrazol-4-yl)-methane. Di-[3,5-dimethyl-1-(2'-cyanoethyl)-pyrazol-4-yl]-methane (6.2 g) was heated in a test tube at 280-300° for 1 hour. The residue was crystallized from methanol; weight 3 g (75%). M.p. 299-303° (in a sealed capillary).

Found %: C 64.66, 64.38; H 8.15, 8.14.  $\text{C}_{11}\text{H}_{16}\text{N}_4$ . Calculated %: C 64.66; H 7.90.

The IR spectrum showed the presence of intense NH group vibrations in the 3100  $\text{cm}^{-1}$  region.

Dipicrate, m.p. 259-262° (from methanol).

Found %: N 20.97, 20.89.  $\text{C}_{11}\text{H}_{16}\text{N}_4 \cdot 2\text{C}_6\text{H}_3\text{O}_7\text{N}_3$ . Calculated %: N 21.18.

On cyanoethylation of this di-(3,5-dimethylpyrazol-4-yl)-methane in a tube (170°, 5 hours), a 37% yield of di-[3,5-dimethyl-1-(2'-cyanoethyl)-pyrazol-4-yl]-methane was obtained. M.p. 159-160°; it gave no depression of the melting point with the above-described preparation.

3,5-Dimethyl-1-(3'-aminopropyl)-pyrazole. A solution of 29.8 g of 3,5-dimethyl-1-(2'-cyanoethyl)-pyrazole in 50 ml of anhydrous methanol was saturated with dry ammonia and hydrogenated in an autoclave over 5 g of skeletal nickel [7] at 120° and 100 atm. After 3 hours, the theoretically required amount of hydrogen had been absorbed. The reaction mass was fractionated in vacuum, after separation of the catalyst. A yield of 24.7 g (82%) of the amine was obtained, with b.p. 130-131° (15 mm),  $n_D^{20}$  1.4987,  $d_D^{20}$  0.9991. The IR spectrum showed the presence of intense NH group vibrations in the 3200  $\text{cm}^{-1}$  region.

Found %: C 62.89, 62.74; H 9.90, 9.78.  $\text{C}_8\text{H}_{15}\text{N}_3$ . Calculated %: C 62.72; H 9.87.

Dipicrate, m.p. 196-198° (from methanol).

3,5-Diphenyl-1-(3'-aminopropyl)-pyrazole. This was obtained by the hydrogenation of 0.05 g-mole of 3,5-diphenyl-1-(2'-cyanoethyl)-pyrazole by the method described above, with a yield of 67%.

B.p. 280-282° (18 mm), very viscous glassy liquid.

Found %: C 77.54, 77.53; H 6.93, 6.90.  $\text{C}_{18}\text{H}_{19}\text{N}_3$ . Calculated %: C 77.93; H 6.90.

Picrate, m.p. 171-172° (from anhydrous methanol).

Found %: C 56.69, 56.60; H 4.69, 4.58.  $\text{C}_{18}\text{H}_{19}\text{N}_3 \cdot \text{C}_6\text{H}_3\text{O}_7\text{N}_3$ . Calculated %: C 56.89; H 4.37.

3,5-Diphenyl-4-chloropyrazole. A solution of 8.8 g of 3,5-diphenylpyrazole in 100 ml of absolute ether was saturated with dry hydrogen chloride. The hydrochloride separating out was filtered off with suction and dissolved in 25 mm of acetic acid, and 20 ml of 33% hydrogen peroxide was added. Then the reaction mass was heated to 80° and left for a day. After neutralization with ammonia solution, the 3,5-diphenyl-4-chloropyrazole was filtered off with suction and recrystallized from a mixture of benzene and petroleum ether. Yield 9 g (70.5%), m.p. 179-180°.

Found %: N 11.38, 11.27.  $C_{15}H_{11}N_2Cl$ . Calculated %: N 11.00.

**3,5-Diphenyl-4-bromopyrazole.** To a suspension of 3,5-diphenylpyrazole in 200 ml of water, 15 g of sodium acetate and then a solution of 5 ml of bromine in 10 ml of acetic acid were added. After half an hour's mixing, the 3,5-diphenyl-4-bromopyrazole was filtered off with suction and crystallized from alcohol. Yield 25 g (83%), m.p. 173-175°.

Found %: N 9.61, 9.58.  $C_{15}H_{11}N_2Br$ . Calculated %: N 9.36.

**Thermal decomposition of 3,5-dimethyl-1-(2'-cyanoethyl)-pyrazole methiodide.** A mixture of 14.9 of 3,5-dimethyl-1-(2'-cyanoethyl)-pyrazole and 17 g of methyl iodide was slowly heated in a 50 ml Favorskii flask with a 25 cm fractionating column surrounded with a glass jacket. On slow distillation, after the methyl iodide had been distilled off, 2.9 g of acrylonitrile, and then, at 150-180°, 8.8 g (80%) of 1,3,5-trimethylpyrazole were obtained. After redistillation the latter had b.p. 171-174° (750 mm).

Picrate, m.p. 148° (from alcohol) [9].

**Cyanoethylation of 3(5)-methyl-5(3)-phenylpyrazole.** A mixture of 7.9 g of 3(5)-methyl-5(3)-phenylpyrazole and 6 g of freshly-distilled acrylonitrile was heated in an autoclave at 160° for 5 hours. The reaction mass was treated with a mixture of 10 ml of ether and 30 ml of petroleum ether and cooled to -10°. After separation, 6.8 g of crystals with m.p. 42-60° were obtained; picrate, m.p. 152° (from methanol). After recrystallization of the main mass of crystals from a small amount of methanol, 5.7 g of 1-(2'-cyanoethyl)-3-methyl-5-phenylpyrazole was obtained, with m.p. 65-67° (not changed after further recrystallizations). NH group vibrations in the 2900-3600  $cm^{-1}$  region were absent from the IR spectrum.

Found %: C 73.86, 73.82; H 6.38, 6.31.  $C_{13}H_{13}N_3$ . Calculated %: C 73.89; H 6.20.

Picrate, m.p. 154-155° (from alcohol).

Found %: C 51.35, 51.33; H 3.54, 3.53.  $C_{13}H_{13}N_3 \cdot C_6H_5O_7N_3$ . Calculated %: C 51.81; H 3.67.

After removal of the first portion of crystals (6.8 g), the filtrate was evaporated to dryness, and from the residual noncrystalline oil (3.1 g) 5.4 g of a picrate was obtained, which was subjected to fractional crystallization from 30% alcohol. A picrate with m.p. 153-154°, identical with the picrate of 1-(2'-cyanoethyl)-3-methyl-5-phenylpyrazole (2.8 g) and the picrate of 1-(2'-cyanoethyl)-3-phenyl-5-methylpyrazole (more soluble in alcohol), with m.p. 131°, (0.8 g) were obtained.

Found %: C 51.57, 51.42; H 3.60, 3.49.  $C_{13}H_{13}N_3 \cdot C_6H_5O_7N_3$ . Calculated %: C 51.81; H 3.67.

#### SUMMARY

Conditions for the cyanoethylation of pyrazoles at the NH group of the nucleus and for the removal of the cyanoethyl group introduced have been worked out. The applicability of the method of cyanoethyl "protection" for certain reactions has been shown.

It has been found that the pyrazole nucleus is not affected under the conditions of hydrogenation of the nitrile group.

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# AROMATIC FLUORINE DERIVATIVES

## VIII\*. REACTION OF CHLORONITRO COMPOUNDS WITH FLUORIDES OF THE ALKALI METALS

N. N. Vorozhtsov, Jr., and G. G. Yakobson

The D. I. Mendeleev Moscow Chemical and Technological Institute

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Aromatic fluorine derivatives containing substituents of a second type in the ortho- and para-positions to the fluorine atom may be obtained by heating the corresponding chlorine derivatives to 170-200° with potassium fluoride in the absence of solvents [1, 2]. Using 2,4-dinitrochlorobenzene as an example it has been shown that the reaction does not proceed with lithium and sodium fluorides either in the absence of a solvent [1, 3] or in nitrobenzene [4] or dimethylformamide [5]. At the same time, rubidium and cesium fluorides are considerably more active fluorinating agents than potassium fluoride [3].

Cesium fluoride may also be used to obtain fluorine derivatives of mononitrobenzene from the o- and p-chloronitro compounds. These compounds do not react with potassium fluoride in the absence of a solvent. By heating chloronitro derivatives of benzene with cesium fluoride for 25 hours at 190-200°, we have obtained o- and p-fluoronitrobenzene, 2,4,5-trifluoronitrobenzene (from 2,4-dichloro-5-fluoronitrobenzene) and 2,4-difluoro-5-chloronitrobenzene (from 2,4,5-trichloronitrobenzene) in good yields.

TABLE 1

Fluoride	Degree of conversion of the chloro derivative (in %)		
	o-Nitrochlorobenzene (200°, 15 hours)	2,4-Dinitrochlorobenzene (195°, 2 hours)	2,4,6-Trinitrochlorobenzene (180°, 5 hours)
LiF	Does not react	Does not react	4
NaF	Does not react	Does not react	17
KF	Does not react	51	92
RbF	6	88	—
CsF	80	98	—

Comparison of the exchange capacity of the fluorides of different alkali metals was carried out for their reaction with o-nitrochlorobenzene, 2,4-dinitrochlorobenzene, and 2,4,6-trinitrochlorobenzene. The results of the experiments are given in Table 1.

Pure 2,4,6-trinitrofluorobenzene was isolated from the reaction mass obtained by the interaction of picryl chloride and potassium fluoride under the conditions indicated in Table 1. Previously, according to patent data, this compound had been obtained in impure form by heating picryl chloride with sodium fluoride in acetic acid [6].

It follows from the data of Table 1 that the reactivity of the fluorides of the alkali metals increases in the sequence:



\*Communication VII, see *ZhOKh*, 31, 1561 (1961).

We found the same behavior also on carrying out the reaction in dimethylformamide [3]. Wallenfels and Draber [7] have shown that in the reaction with chloranil the exchange capabilities of cesium fluoride considerably exceed those for potassium fluoride. Sodium fluoride undergoes practically no reaction with chloranil. However, such a large difference in behavior of potassium and sodium fluorides has been repeatedly noted in their action on chloro derivatives of the aliphatic series [8].

Thus, on heating chloroacetone with potassium fluoride in ethylene glycol, fluoroacetone is formed in 65% yield. Under the same conditions, 4% of the chloro derivative reacts with sodium fluoride, and only 0.4% with lithium fluoride [9].

The increase in the reactivity of the alkali metal fluorides with an increase in the atomic weight of the metal is confirmed by the increase in the rate of isotope exchange of fluorine between alkyl fluorides and metal fluorides in the K-Cs series. Lithium and sodium fluorides undergo practically no reaction [10].

TABLE 2. Fluorine Derivatives Obtained by the Action of Cesium Fluoride on Chlorine Derivatives

Fluorine derivative	Yield (%)	Boiling point*	$n_D^*$
o-Fluoronitrobenzene	80-88	214-216° at 750 mm (215° at 766 mm [12])	1.5342 at 16° (1.5323 at 17.3 [12])
p-Fluoronitrobenzene**	70-80	203-205 at 755 mm (205° [12])	—
2,4,5-Trifluoronitrobenzene***	68-72	194-195 at 755 mm (192° [13])	1.4949 at 17° (1.4938 at 20° [13])
2,4-Difluoro-5-chloronitrobenzene****	65-70	110-111 at 17 mm (105° at 15 mm [14])	1.5350 at 18° (1.5337 at 20° [14])

The fluorides of the metals of group II of D. I. Mendeleev's periodic system have been found to be unsuitable as reagents for replacing chlorine by fluorine. Thus, according to our results, 2,4-dinitrochlorobenzene remains unchanged on 5 hours' heating at 200° with calcium, barium, and zinc fluorides.

The experimental results permit some hypotheses on the causes of the increase in reactivity of the fluorides of the alkali metals with an increase in the atomic weight of the metal to be put forward:

On heating with chloronitro compounds, the metal fluorides do not dissolve in them appreciably. It is probable, however, that the reaction nevertheless takes place in solution. In this case, either the fluorine ion or an ion pair of the metal fluoride may react with the chloro derivative. In the first case, the difference in the rate of reaction is explained by the different concentrations of fluorine ion, depending on the solubility of MeF (Me represents an alkali metal) in the reaction mixture and the degree of its dissociation. However, if the chloro derivative reacts with the ion pair MeF, the change in the rate of formation of the fluorine derivative on the action of the fluorides of various metals will depend on the solubility of MeF in the reaction mixture and the degree of polarization of the ion pair, which rises in the series Li-Cs.

A more detailed consideration of the causes of the dependence of the rate of replacement of chlorine by fluorine on the atomic rate of the metal will be undertaken after additional data have been obtained.

#### EXPERIMENTAL PART

Rubidium and cesium fluorides. After carrying out the reaction, the salts were heated for 2 hours in a platinum crucible at 300-350°, finely ground, and again heated for 2 hours at 250-300°. The hot products were rapidly transferred to the reaction flask heated to 100-120°.

\* Literature data are given in brackets.

\*\* M.p. 24.5-25°, (27° [12]).

\*\*\* From 2,4-dichloro-5-fluoronitrobenzene.

\*\*\*\* From 2,4-5-trichloronitrobenzene.



Preparation of fluorine derivatives by the action of cesium fluoride. A mixture of 20 g-moles of the chloronitro compound and 23-25 g-mmoles of cesium fluoride (or 45-50 g-mmoles of CsF for the replacement of two chlorine atoms) was heated in a three-necked flask fitted with a stirrer and reflux condenser protected with a magnesium perchlorate tube, for 25 hours at 190-200°. To prevent the access of moisture, the reaction was carried out in a current of nitrogen successively passed over phosphorus pentoxide and fused caustic potash. The reaction mixture was treated with hot benzene and filtered. The residue was washed several times on the filter with hot benzene. The benzene was distilled off, and the residue was distilled in a fractionating column with a glass packing. The results of the experiments are given in Table 2.

Reduction of the fluoronitro compounds with hydrogen over skeletal nickel by the method described earlier [11] yielded fluoroanilines, the acetyl derivatives of which exhibited no depression of the melting point in admixture with known products.

Preparation of picryl fluoride. A mixture of 1.24 g of picryl chloride and 0.35 g of anhydrous potassium fluoride was heated at 185° for 5 hours in a three-necked flask fitted with a stirrer and an air condenser protected with a calcium chloride tube. The reaction mixture was treated with 20 ml of benzene and filtered. The residue on the filter was washed with benzene (three 5-ml portions). After evaporation of the benzene, 0.76-0.86 g (66-75%) of picryl fluoride was obtained in the form of pale yellow needles with m.p. 127.5-128.5° (from a mixture of benzene and petroleum ether). According to data in the literature, it forms a dark brown mass with m.p. 150-160° [6].

Found %: N 17.94; 18.14; F 7.9; 7.9.  $C_6H_2O_6N_3F$ . Calculated %: N 18.18; F 8.2.

Comparison of the reactivity of the metal fluorides. A mixture of 10 g-mmoles of the chloronitro compound and 12 g-mmoles of anhydrous metal fluoride was heated in a 10 ml three-necked flask fitted with a stirrer and reflux condenser protected with a calcium chloride tube. The experiments with rubidium and cesium fluorides were carried out in a current of nitrogen purified by the method described above. After completion of the reaction, the reaction mixture was treated with 20 ml of hot anhydrous benzene and filtered. The residue was washed with hot benzene (three 5 ml portions), after which it was dissolved in 200 ml of distilled water. The amount of ionic chlorine liberated in the reaction was determined by titration using Volhard's method.

#### SUMMARY

1. A method for obtaining aromatic fluoronitro compounds containing nitro groups in the ortho- and para- positions to the fluorine atom by the action of cesium fluoride on the chlorine derivatives at 190-200° has been developed.
2. Picryl fluoride has been obtained by the action of potassium fluoride on picryl chloride at 185°.
3. It has been shown that the rate of replacement of chlorine by fluorine when aromatic chloronitro compounds react with alkali metal fluorides rises with an increase in the atomic weight of the metal.

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AN INVESTIGATION OF THE STRUCTURE OF SOME  
DERIVATIVES OF 2-MERCAPTOBENZOTHAZOLE  
BY THE DIPOLE MOMENT METHOD

E. N. Gur'yanova, I. I. Éitingon, M. S. Fel'dshtein,

I. G. Chernomorskaya, and B. A. Dogadkin

Scientific Research for Tire Manufacturing and the L. Ya.

Karpov Physico-Chemical Institute

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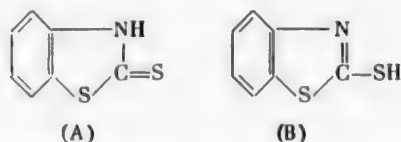
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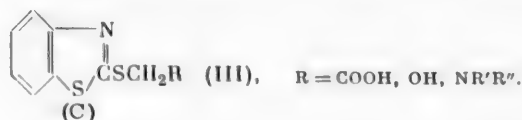
A series of aminomethyl, hydroxy-, and carboxymethyl derivatives of 2-mercaptobenzothiazole [1, 2] were recently synthesized and investigated for use as accelerators of the vulcanization of rubber.

It appeared interesting to inquire to what degree the striking changes of vulcanizing activity of these derivatives of 2-mercaptobenzothiazole are associated with the peculiarities of their structures.

It is known that 2-mercaptobenzothiazole in the crystalline condition and in indifferent solvents has the thione structure (A) [3, 4, 5], although under certain conditions it gives derivatives of the tautomeric form (B).



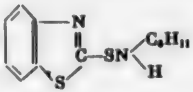
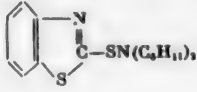
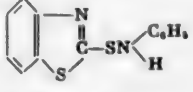
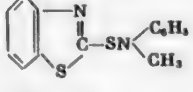
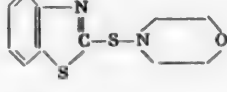
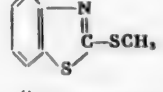
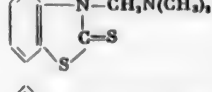
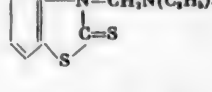
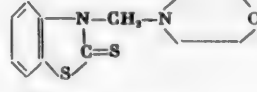
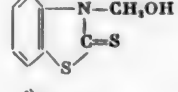
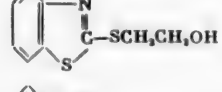
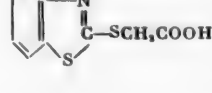
It is not always possible to establish the structure of a product compound as an S- or N-derivative. The S-substituted structure was ascribed to a series of compounds related to the aminomethyl derivatives of 2-mercaptobenzothiazole on the basis of chemical data [6]. The results of a spectroscopic investigation of the same compounds in the ultra-violet region indicated that the compounds had the N-substituted structure [7]. On the basis of chemical data it was shown in a recently published article [8] that the aminomethyl derivatives of 2-mercaptobenzothiazole are N-substituted compounds. The compounds investigated in researches completed with the participation of some of us [1, 2] were considered as S-substituted 2-mercaptobenzothiazoles, and to them were ascribed the structure (C).



An investigation of the spectrum of diethylaminomethyl-2-thiobenzothiazole in the vibration region of the C=S bond ( $6.7\text{--}7.2\ \mu$ ) served to some degree as a basis for this. However, it should be observed that the vibration frequency of the C=S bond is not sufficiently characteristic. It undergoes a considerable displacement depending on the structure of the molecule [9], therefore an investigation over the narrow spectral region (approximately  $70\ \text{cm}^{-1}$ ) is not sufficient for a proven conclusion about the structure of such compounds.

The dipole moment method is a very effective method for the investigation of the structure of derivatives of 2-mercaptobenzothiazole. The polar properties of the molecules possessing configurations (A) or (B) are different. The maximum value of the dipole moment calculated according to the vector sum for the structure (B) was  $2\text{--}2.4\text{D}$ , and for the structure (A)  $\text{--}4.4\text{--}4.6\text{D}$  [4]. The dipole moment of the S-methyl derivative of 2-mercaptobenzothiazole (B) was equal to  $1.4\text{D}$ , that of the N-methyl derivative (A)  $\text{--}4.84\text{D}$  [10]. The dipole moments of a series of derivatives

TABLE\*. Dipole Moments

The No. of the compound	Compound	M.p.	$P_{\infty}$	$R_D$	$\mu \cdot 10^{-17}$
(I)		103—104°	246.0	75.6	2.87
(II)		92—93	288.5	101.4	3.01
(III)		123	190.8	74.1	2.38
(IV)		94—96	202.9	89.1	2.44
(V)		83	130.3	68.3	1.73
(VI)		47—48	88.44	51.5	1.33
(VII)		79—80	463.9	64.3	4.39
(VIII)		87—88	470.8	73.5	4.38
(IX)		145—147	533.4	73.0	4.72
(X)		128—129	486.4	52.6	4.58
(XI)		—	169.2	57.3	2.33
(XII)		153—155	461.9	54.8	4.44

\* $P_{\infty}$  is the molar polarization of the substance at infinite dilution, the extrapolation to infinite dilution being carried out according to the method of Hedebrand;  $R_D$  is the molar refraction, calculated according to the additive for the sodium D line;  $\mu$  is the dipole moment calculated according to the formula  $\mu = 0.0128\sqrt{T} \cdot \sqrt{R_{\infty} - R_D}$ .

of 2-mercaptobenzothiazole are reported in this paper for the purpose of establishing the structures of such compounds (table).

All of the compounds investigated were synthesized by us and after purification had the constants cited in the table. The measurement of the dipole moments were carried out in benzene at 25°.

The results of the comparison of the experimental values of the dipole moments with those calculated according to the vector sum, in particular for the series of sulfenamide vulcanization accelerators (I-V), confirmed the generally accepted structures of these compounds. The small variation in the magnitudes of the dipole moments—from 2.38D for 2-benzothiazolesulfenamide (III) to 3.01D for compound (II) are dependent basically on differences of the dipole moments of the respective amino groups. This also explains the lowering to 1.73D in 2-benzothiazolesulfenmorpholide (V) in comparison with the other sulfenamides.

The dipole moment of 2-methylmercaptobenzothiazole was 1.33D. It was previously reported [10] that the dipole moment of this substance was 1.40D.

The replacement of one of the hydrogen atoms of the methyl group of 2-methylmercaptobenzothiazole by the dialkylamino groups  $N(CH_3)_2$  or  $N(C_2H_5)_2$  must lead to an increase of the dipole moment of these compounds to 2-2.5D. Consequently, if the aminomethyl derivatives (VII-IX) are S-substituted, then their dipole moments should be equal to 2-2.5D. They are experimentally found to be approximately 4.4D. The greater magnitude of the dipole moment indicates that these compounds have some other structure.

On the basis of a comparison of the experimental values of the dipole moments with those calculated according to the additive scheme one arrives at the conclusion that the compounds (VII-IX) are not S-, but N-substituted 2-mercaptobenzothiazoles. This conclusion is in agreement with the data of [8].

The investigation of the structure of the hydroxymethyl and hydroxyethyl derivatives of 2-mercaptobenzothiazole (X, XI) was interesting. The vulcanizing activities of these compounds are sharply different [1]. The hydroxymethyl derivative (X) is an active accelerator of vulcanization, while the hydroxyethyl derivative has practically no activity. The dipole moments of these compounds also turned out to be different. The hydroxymethyl derivative (X) is the N-substituted compound, i.e., N-hydroxymethylbenzothiazolethione-2 with dipole moment 4.58D, while the hydroxyethyl derivative—ans S-substituted 2-mercaptobenzothiazole has the dipole moment 2.33D.

The comparatively large value of the dipole moment (4.44D) of the compound (XII) is explained by the presence of the large moment of the carboxyl group.

Thus, on the basis of measurements of the dipole moments it has been established that the derivatives of 2-mercaptobenzothiazole which we have investigated have different structures. The compounds (I-VI, XI, XII) are S-substituted derivatives of 2-mercaptobenzothiazole, and the compounds (VII-X) are N-substituted derivatives. This is confirmed by the synthesis of these compounds; the S-substituted compounds were obtained by the interaction of the sodium salt of 2-mercaptobenzothiazole with methyl iodide, ethylene chlorohydrin and the sodium salt of chloroacetic acid respectively for the compounds (VI, XI, and XII). The N-benzothiazolethione derivatives were obtained by the interaction of 2-mercaptobenzothiazole with formalin in a basic medium, and also by condensation with formalin and the respective amine (compounds VII-X).

The variation in the vulcanizing activity of these compounds is explained by their different structures [1, 2, 11]

#### SUMMARY

The dipole moments of a series of derivatives of 2-mercaptobenzothiazole which vary sharply in their activities as accelerators of the vulcanization of rubber were measured. It was shown that some of the compounds studied possessed the 2-mercaptobenzothiazole structure and others are derivatives of the 2-thione form.

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# THE SYNTHESIS OF CHELANTS IN A SERIES OF AZOXY COMPOUNDS

## III. THE SYNTHESIS OF (6''-Hydroxy-3''-methylphenylazoxy)- benzene-(2'-azo-1)-2-naphthol

V. M. Dziomko and K. A. Dunaevskaya

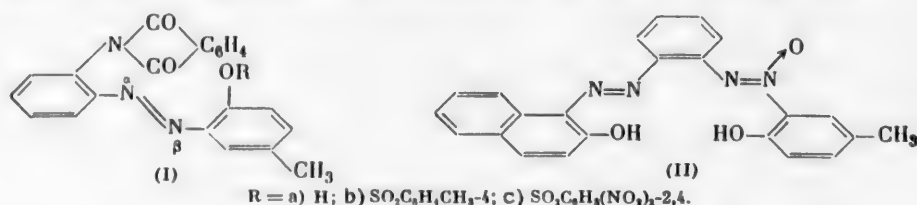
The All-Union Scientific Research Institute for Chemical Reagents

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Original article submitted November 22, 1961

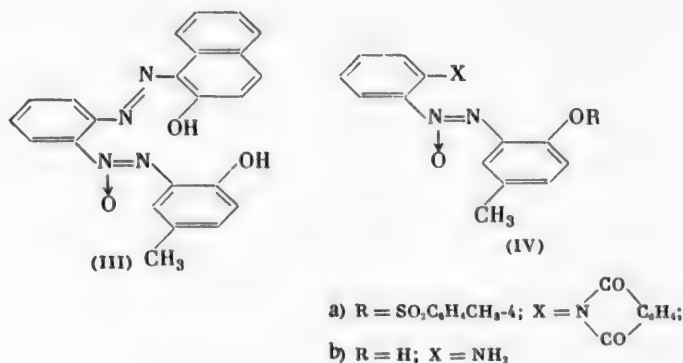
We previously reported on the synthesis of 2'-hydroxy-5'-methylbenzene-(1'-azoxy-1)-benzene-(2-azo-1'')-2''-hydroxynaphthalene [1]. It was later established [2] that the oxidation of compound (Ia) yielded only the  $\beta$ -isomer of the corresponding azoxy compound. From the method of synthesis [1], one may ascribe the structure 2-[2''-hydroxynaphthalene-(1''-azo-2')-phenylazoxy]-4-methylphenol (II) to the compound cited above.



On the basis of the results of [3] the tosyl derivative (Ib) was subjected to oxidation for the purpose of synthesizing the isomeric (6''-hydroxy-3''-methylphenylazoxy)-benzene-(2'-azo-1)-2-naphthol (III). After hydrazinolysis and basic hydrolysis, the 2-(6'-hydroxy-3'-methylphenylazoxy)-aniline (IVb) which was isolated as the unstable hydrochloride salt was diazotized and coupled with 2-naphthol. The compound (IVb) in alkaline alcoholic solution gave a definite positive reaction [3] for an  $\alpha$ -isomer of an ortho-hydroxyazoxy compound.

The new compound (III) differs significantly in physical and chemical properties from the  $\beta$ -isomer (II).

Only an insignificant quantity of azoxy compound is formed by the oxidation of the 2-4-dinitrobenzenesulfonyl derivative (Ic) (cf [3]).





## EXPERIMENTAL PART

2-Hydroxy-2'-phthaloylamino-5-methylazobenzene (Ia). This was synthesized by coupling the diazo compound from 2-amino-1-phthaloylaminobenzene with p-cresol in alcoholic soda solution. It was purified by recrystallization from acetic acid. M.p. 160-162° [1].

2'-Phthaloylamino-2-(p-toluenesulfonyloxy)-5-methylazobenzene (Ib). To a solution of 4.0 g of the compound (Ia) in 100 ml of acetone was added 7 ml of 20% NaOH, and then 6 g of p-toluenesulfonyl chloride was added in small portions with stirring during 5-10 min; the mixture was stirred for 2-3 hrs at room temperature. The product was filtered off and crystallized from acetone (120 ml).

The yield was 3.0 g (52.6%). M.p. 194°. It was an orange powder quite soluble in ethyl and methyl alcohols, poorly soluble in water.

Found %: N 8.17, 8.30.  $C_{28}H_{21}O_5N_3S$ . Calculated %: N 8.20.

2'-Phthaloylamino-2-(2,4-dinitrobenzenesulfonyloxy)-5-methylazobenzene (Ic). This was obtained in the same fashion as 2'-methyl-2-(2''-4''-dinitrobenzenesulfonyloxy)-5-methylazobenzene and 2'-bromo-2-(2'',4''-dinitrobenzenesulfonyloxy)-5-methylazobenzene [3]. The yield was 1.9 g (29.2%). M.p. 159-160°. It was an orange powder soluble in acid and in toluene, poorly soluble in alcohol and petroleum ether.

Found %: N 11.68, 11.64.  $C_{27}H_{17}O_9N_5S$ . Calculated %: N 11.90.

(6''-Hydroxy-3''-methylphenylazoxy)-benzene-(2'azo-1)-2-naphthol (III). To a solution of 2.5 g of the compound (Ib) in glacial acetic acid (200 ml) was added 25 ml of 30% hydrogen peroxide and the mixture was heated for 60 hrs at 75-80°, 20 ml of 30% hydrogen peroxide being added after each 20 hr period.

After cooling and filtering, the solution was poured over ice (200 g); the product was washed on the filter with distilled water, and dried in the dark. The weight of the air-dried solid was 1.25 g. It was dissolved in 80 ml of alcohol, 0.8 g of hydrazine hydrate was added, the mixture was heated for 15 hrs at 75-80°, 80 ml of concentrated hydrochloric acid was added, and the mixture was heated for an additional 6 hrs. After filtration and dilution with water (approximately 30 ml), sodium carbonate was added until a neutral reaction was obtained; the tarry precipitate which separated was filtered off, dissolved in a mixture of 100 ml of acetone, 100 ml of methanol, and 100 ml of water; 4 g of KOH were added and the solution was boiled for 18 hrs. The filtered solution was evaporated to  $\frac{1}{3}$  its original volume, neutralized by saturation with carbon dioxide, and extracted with chloroform (two 30 ml portions). The extract after drying over sodium sulfate was saturated with dry hydrogen chloride. The precipitate which formed after the addition of petroleum ether (100 ml) was filtered off and washed with petroleum ether (approximately 25-30 ml). The yield of the hydrochloride salt of compound (IVb) was 0.1 g (8.7%). The compound (IVb) in an alkaline alcoholic solution gave a definite positive reaction [3] for the  $\alpha$ -isomer of an ortho-hydroxyazoxy compound.

To a solution of 0.1 g of the hydrochloride salt of compound (IVb) in 30 ml of alcohol was added 10 ml of concentrated hydrochloric acid; 0.3 g of sodium nitrite in 10 ml of water was added with stirring at a temperature of 0-3°. The diazo solution thus obtained and an aqueous solution of sodium carbonate (10.0 g in 50 ml of water) were simultaneously and gradually added with stirring to a solution of 0.06 g of  $\beta$ -naphthol in a mixture of 40 ml of 20% NaOH and 20 ml of alcohol. The reaction mixture was let stand 1 hr at 0-3°. After acidification with hydrochloric acid (to Congo), the precipitate which separated was filtered off, washed with water, reprecipitated with acid from alcoholic alkali, and crystallized from a mixture of 15 ml of alcohol and 1.5 ml of chloroform.

The yield was 0.0127 g [9.07% on the basis of compound (IVb), 0.79% on the basis of compound (Ib)]. M.p. 201-202°. The red powder was quite soluble in organic solvents, poorly soluble in water. In contrast to compound (II), compound (III) did not form a product with calcium, soluble with difficulty in chloroform. The mixture with the compound (II) melted at 196.6°.

Found %: N 14.18, 14.50.  $C_{25}H_{18}O_3N_4$ . Calculated %: N 14.07.

In an ascending chromatogram in 96% alcohol on paper "slow, for chromatography", the  $R_f$  of compound (II) was 0 and that of compound (III) was 1.0.

The oxidation of 2'-phthaloylamino-2-(2'',4''-dinitrobenzenesulfonyloxy)-5-methylazobenzene (Ic). The starting material (Ic) was regenerated in 53.3% yield (0.8 g) by oxidation according to the method [3].

A precipitate was isolated from the filtrate which was worked up in a fashion similar to the product of oxidation (Ib) (see above). Only traces of compound (II) were isolated in this case.

# SUMMARY

(6'-Hydroxy-3'-methylphenylazoxy)-benzene-(2'-azo-1)-2-naphthol was synthesized.

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# STEROIDS

## XV. THE SYNTHESIS OF CORTISONE ACETATE

### FROM PREGNANDIOL-3 $\alpha$ , 17 $\alpha$ -DIONE-11,20\*

N. N. Suvorov, L. V. Sokolova, Z. A. Yaroslavtseva,

Zh. D. Ovchinnikov, V. S. Murasheva, and F. Ya. Leibel'man

The S. Ordzhonikidze All-Union Scientific Research Chemico-Pharmaceutical Institute

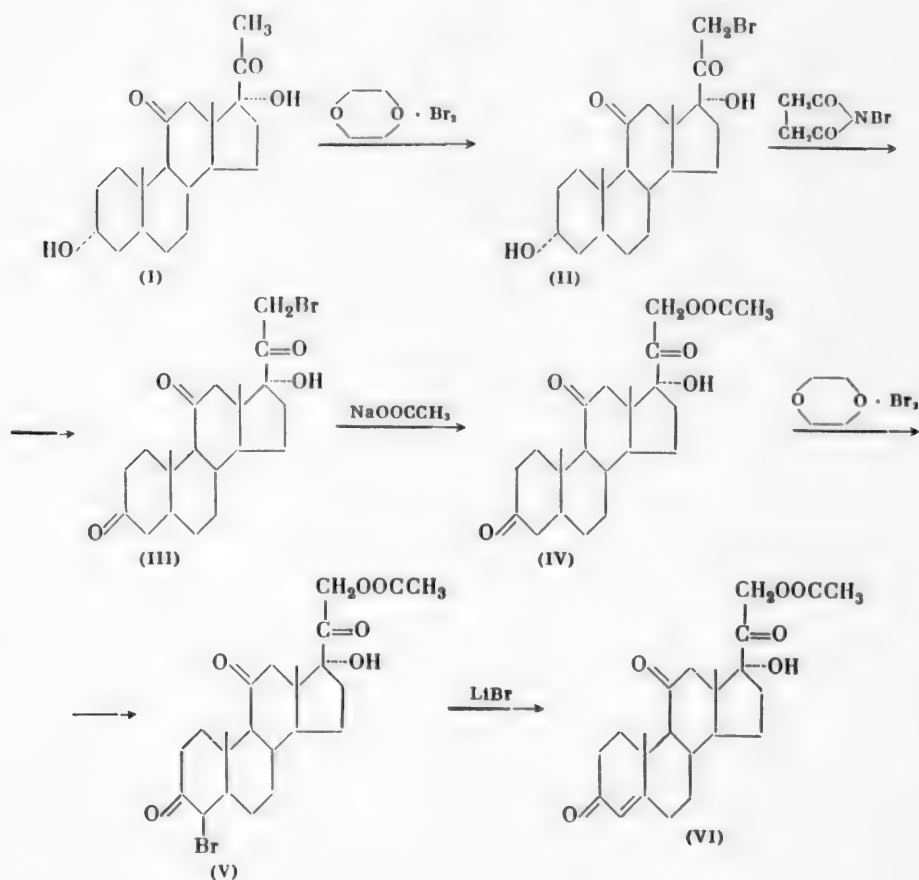
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We reported earlier the general features of our synthesis of cortisone acetate from solasodine through progesterone and 11 $\alpha$ -hydroxyprogesterone [6]. The individual steps of this transformation have been described in greater detail [2, 7-10]. The experimental details relating to the final step of the synthesis—the conversion of pregnandiol-3 $\alpha$ , 17 $\alpha$ -dione-11,20 (I) into cortisone acetate—are set out in the present article.

This conversion was realized by a new scheme, different from that previously described [11, 12].



\* Communications X-XIV, see [1, 5].

Bromination in positions 4 and 21 was carried out with dioxane dibromide, first suggested for the bromination of ketones by A. P. Terent'ev and L. A. Yanovskaya [13]. The oxidation of (II) was conducted with N-bromosuccinimide in methanol; the exchange of bromine in position 21 for the acetoxy group was accomplished with sodium acetate in dimethylformamide. Finally, the dehydrobromination of (V) to form cortisone acetate was carried out by methods described in the literature [14, 15].

The over-all yield of cortisone acetate from  $11\alpha$ -hydroxyprogesteron was 17.8%, from solasodine—6.2%.

#### EXPERIMENTAL PART

##### 21-Bromopregnandiol-3 $\alpha$ , 17 $\alpha$ -dione-11, 20 (II).

a) The preparation of dioxane dibromide. To a mixture of 68 ml of dioxane and 74 ml of heptane which was cooled with ice was added a cooled solution of a mixture of 141.6 g of bromine and 144 ml of heptane; the flask containing the reaction mixture was cooled in an ice bath while the contents were stirred for 5 min. The orange precipitate was filtered off, washed twice with 20 ml of heptane, and dried on the funnel with a stream of air for 5-6 min. The dioxane dibromide (150 g) was immediately used for the reaction.

b) Bromination. Three liters of methanol and 200 g of pregnandiol-3 $\alpha$ , 17 $\alpha$ -dione-11,20 (I) were placed in a three-necked flask furnished with a stirrer, thermometer, and dropping funnel. A solution of 142.6 g of dioxane dibromide in 0.5 liters of methanol was added drop-wise to the transparent solution at room temperature (18-20°) at the rate of decolorization. The period for bromination was 4-5 hrs. The solution was poured into a separatory funnel, diluted with 7 liters of chloroform, and washed with a cool solution of 23.5 g of sodium hydroxide in 5.2 liters of water. As long as the aqueous layer gave a neutral reaction with litmus, the chloroform layer was separated from the aqueous layer and the latter was extracted twice with chloroform. The combined chloroform extracts were evaporated in vacuo at 25-30° to a volume 700-800 ml, and this was let stand at 5-6° for 3-4 hrs. The precipitate was filtered off, washed with a cooled mixture of 200 ml of ether and 100 ml of chloroform, and then dried to constant weight. The yield of the bromide (II) was 178 g (72.5%), m.p. 192-194° (dec.),  $[\alpha]_D^{20} + 61-64^\circ$  (c = 1 in chloroform).

The chloroform-ether mother liquor was evaporated in vacuo at 25-30° to dryness and was subjected to debromination.

c) Debromination. The residue after evaporation of the chloroform and ether from the mother liquor was dissolved in 760 ml of acetic acid and to the solution with stirring and at a temperature not above 30° was added 76 g of zinc dust in small quantities over a period of 20-30 min; stirring was then continued at room temperature for an additional hour. The zinc was separated and washed with acetic acid (100 ml), and the acetic acid solution was poured into a 10-fold quantity of ice water. The precipitate of starting material (I) was dried to constant weight and recrystallized from 600 ml of benzene. The yield of (I) was 47 g, m.p. 198-199°, which could again be brominated.

The yield of the bromoketone (II) in consideration of the recovery of (I) was 95%.

##### 21-Bromopregnanol-17 $\alpha$ -trione-3,11,20 (III).

Six liters of methanol and 200 g of the bromoketones (II) were placed in a three-necked flask furnished with a stirrer. The mixture was stirred at a temperature of 40° until solution was completed; it was then cooled to 20° and 180 g of N-bromosuccinimide and 370 ml of water were added. The reaction mixture was stirred for 24 hrs at room temperature in darkness. At the end of the reaction the precipitated trione (III) was filtered off and washed with cold methanol and with ether. The substance was dried in vacuo at room temperature. The yield was 146 g (73.3%), m.p. 212-215° (dec.),  $[\alpha]_D^{20} + 76^\circ$  (c = 1 in chloroform).

The methanol mother liquor was diluted with 6 liters of water and was placed in a refrigerator for 10 hrs. The precipitate was filtered off and washed with water. An additional 43 g of substance was obtained with m.p. 206-208°, usable for the following steps without purification.

The over-all yield of (III) was 189 g (95%).

##### Dihydrocortisone acetate (IV).

A mixture of 150 g of the trione (III), 1.5 liters of dimethylformamide and 75 g of anhydrous, powdered sodium acetate was placed in a 3-necked flask furnished with a gas tight stirrer, thermometer, reflux condenser, and a tube for the introduction of gas, and was heated with stirring in a current of nitrogen to 60° for 2 hrs. The reaction mixture was cooled to -10°, and to it was added 1.5 liters of ice water; it was then stirred for an additional 30 min at the same temperature. The precipitate was filtered off, washed with ice water, with cold methanol, and with ether. The

dihydrocortisone acetate thus obtained was dried in vacuo at room temperature. The yield was 125 g, m.p. 225-227.5°,  $[\alpha]_D^{20} + 81-87^\circ$  (c=1 in acetone). An additional 5 g of the substance with m.p. 220-222° was obtained from the mother liquor. The over-all yield of (IV) was 130 g (91%).

#### The acetate of 4-bromodihydrocortisone (V).

To a mixture of 150 g of dihydrocortisone acetate (IV), 1.33 liters of dimethylformamide and 3 g of the monohydrate of p-toluenesulfonic acid there was slowly added from a dropping funnel over an 8-10 hr period a solution of 93.6 g of dioxane dibromide in 570 ml of dimethylformamide. The bromination was conducted at 18-20° with artificial illumination; after all of the dioxane dibromide solution had been added a 30 min period was allowed to elapse; 915 ml of water was then added during 20 min, the reaction mixture was cooled to -2°, and let remain at this temperature for 30 min. The precipitate was filtered off and washed twice with ice water, with cold alcohol, and with ether. The bromide thus obtained (125-130 g) was dried at room temperature in vacuo. For purification it was triturated with 435 ml of acetone for 10 min; 1.75 liters of ether was then added, and the mixture was stirred for 10 min; it was allowed to stand for 2 hrs at a temperature of 0-3°. The solid was filtered off and dried in vacuo at room temperature. The yield was 119 g (66%) of the acetate of 4-bromodihydrocortisone with m.p. 183-190° (dec.). The mother liquor after the separation of the bromide was poured into water, the precipitate was filtered off, and together with the substance obtained after evaporation of the alcohol-ether and ether-acetone wash liquors was debrominated with zinc in the same way as described earlier for the preparation of the starting material, dihydrocortisone acetate (IV). The yield of dihydrocortisone acetate was 30 g with m.p. 219-220°C. The yield of the bromide (V) taking into consideration the recovered dihydrocortisone acetate was 83%.

#### Cortisone acetate (VI).

Three grams of anhydrous lithium carbonate and 2.6 g of anhydrous lithium bromide were added with stirring to 35 ml of dimethylformamide while a current of nitrogen was passed; 5.4 g of the bromide (V) was rapidly added, and the mixture was heated at 90-95° for 20 hrs. The reaction mixture was cooled to 3-5° and 130 ml of water containing 13 ml of acetic acid were added; the mixture was let stand for 1 hr at 0 to -5°. The precipitate (4.5 g) was filtered off, washed with water until a neutral reaction was obtained, dried, and recrystallized from methanol. The yield was 3.50 g, m.p. 241-242°. From the mother liquor after additional purification was obtained 0.25 g of the acetate with m.p. 241-242°. The total yield was 3.75 g (83.5%). The same yield was obtained when the work was carried out by the method described in the literature [15].

The cortisone obtained satisfied the requirements of article (IX) of the State Pharmacopoeia of the USSR.

#### SUMMARY

The synthesis of cortisone acetate from pregnandiol-3 $\alpha$ ,17 $\alpha$ -dione-11,20 was carried out through 21-bromopregnanediol-17 $\alpha$ -trione-3,11,20 and dihydrocortisone acetate.

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# THE SYNTHESIS OF DERIVATIVES OF THIAZOLIDONE WHICH HAVE BIOLOGICAL INTEREST

## XVI. THE INFLUENCE OF SUBSTITUENTS IN THE THIAZOLIDONE RING ON THE ULTRA-VIOLET ABSORPTION SPECTRA

N. M. Turkevich and Yu. M. Pashkevich

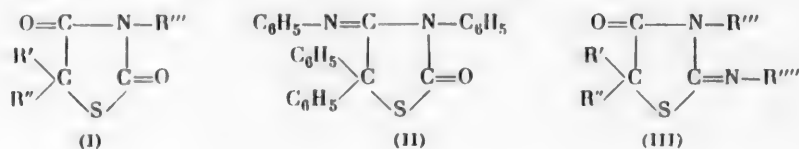
The L'vov Institute of Medicine

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 11,  
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Original article submitted December 24, 1960

The introduction of arylidene groups into the 5-position of derivatives of thiazolidone-4 causes the appearance of a very intense K-absorption band in the region from 350 to 425 m $\mu$  with clearly expressed maxima, which are explained by the presence of the conjugated chain in the molecules of these substances [1, 2]. In order to resolve the question of whether the appearance of this highly intense absorption band depends on the introduction into position-5 of aryl radicals or only of arylidene groups with a conjugated chain, we decided to study the absorption spectra of 5-phenyl derivatives of thiazolidone-4.

The introduction of a single phenyl group into the 5-position of the thiazolidinedione-2,4 molecule (I, R' = C<sub>6</sub>H<sub>5</sub>, R'' = R''' = H) has little influence on the absorption curve (Fig. 1). The absorption spectrum of 5,5-diphenylthiazolidinedione-2,4 (I, R' = R'' = C<sub>6</sub>H<sub>5</sub>, R''' = H) is shifted in the long wave-length direction and is also characterized by a considerably greater intensity. The introduction of third phenyl group (I, R' = R'' = R''' = C<sub>6</sub>H<sub>5</sub>) leads to a further shift of the spectrum in the direction of greater wave-lengths, the increase in the absorption intensity being so strongly expressed that a maximum appears in the amide band at 300 m $\mu$ .



The replacement of the oxygen atom in position 4 by a phenylimino group (3,5,5-triphenyl-4-phenylimino thiazolidinone-4, II) causes the maximum at 300 m $\mu$  to disappear, the latter being transformed into a bulge on the very intense ring band (the short wave-length band of benzene [3]).

Similar phenomena are noted when to phenyl groups are introduced into position 5 or into positions 3 and 2' of the molecule of pseudothiohydantoin (Fig. 2). 2',3,5,5-Tetraphenyl pseudothiohydantoin (III, R' = R'' = R''' = C<sub>6</sub>H<sub>5</sub>) is characterized by the most strongly shifted spectrum in the long wave-length direction. In contrast to this the absorption spectrum of 2',3,5-triphenyl-pseudothiohydantoin (III, R' = H, R'' = R''' = C<sub>6</sub>H<sub>5</sub>) is shifted in comparison to the spectrum of 2',3-diphenyl pseudothiohydantoin (III, R' = R'' = H, R''' = R'''' = C<sub>6</sub>H<sub>5</sub>) toward the short wave-length region.

A decrease of the absorption intensity is observed on the introduction of phenyl groups into positions 3 or 5 of the rhodanine molecule (Fig. 3). A freshly prepared alcoholic solution of 3,5-diphenylrhodanine (IV) is yellow, and has a maximum in the K-band at 408 m $\mu$ . The solution on standing begins to decolorize, the maximum becoming continually less intense.

The previously undescribed 3,5-diphenylrhodanine (IV) was obtained by the condensation of the ethyl ester of  $\alpha$ -chlorophenylacetic acid with potassium phenyldithiocarbamate.



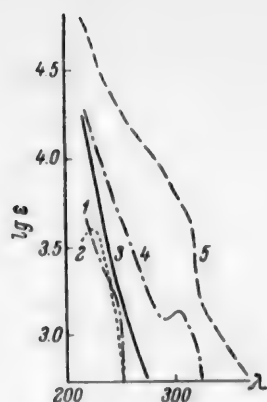


Fig. 1. The spectral absorption curves of derivatives of thiazolidinedione-2,4 (I). 1) 5-Phenyl derivative; 2) unsubstituted; 3) 5,5-diphenyl derivative; 4) 3,5,5-triphenyl derivative; 5) 3,5,5-triphenyl-4-phenyliminothiazolidone-4 (II).

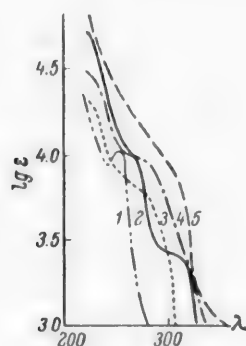
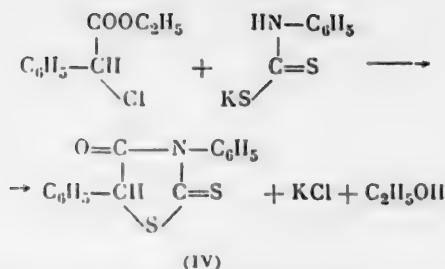


Fig. 2. The spectral absorption curves of the pseudothiohydantoin (III). 1) Unsubstituted; 2) 5,5-diphenyl derivative; 3) 2',3,5-triphenyl derivative; 4) 2',3-diphenyl derivative; 5) 2',3,5,5-tetraphenyl derivative.



This preparation possesses anti-spasmodic activity according to the data of the faculty of Pharmacology of the L'vov Medical Institute (A. A. Gavrilyuk and V. I. Zapadnyuk).

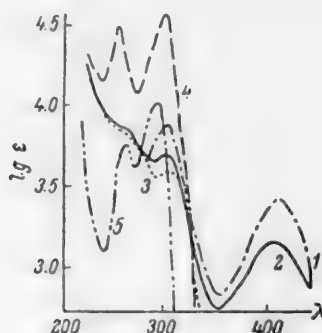


Fig. 3. The spectral absorption curves of rhodanines. 1) 3,5-Diphenylrhodanine (IV) (after 30 min); 2) the same (after 48 hours); 3) the same (after 14 days); 4) unsubstituted rhodanine; 5) triphenylrhodanine.

#### EXPERIMENTAL PART

Syntheses of 5,5-diphenyl- and 3,5,5-triphenylthiazolidinedione-2,4,5,5-diphenyl- and 2',3,5,5-tetraphenyl pseudothiohydantoin, and also 3,5,5-triphenyl-4-phenyliminothiazolidone-2 have been described earlier [4].

**3,5-Diphenylrhodanine (IV).** A mixture containing 0.02 g-mole each of aniline, carbon disulfide, and KOH was shaken with 15 ml of water for 30 min during which time the precipitation of potassium phenyldithiocarbamate was observed. To the product was added 0.02 g-moles of the ethyl ester of  $\alpha$ -chlorophenylacetic acid; the mixture was shaken for 30 min, and then was boiled

under reflux for 3.5 hrs with 15 ml of concentrated hydrochloric acid. The oily phase which was initially formed rapidly began to crystallize. The precipitate was filtered off, washed with water, dried, and purified by trituration with ether. The yield was 1.3 g (22.8% of a yellow crystalline substance with m.p. 174° (from alcohol).

Found %: C 63.39, H 4.02; N 5.13.  $\text{C}_{15}\text{H}_{11}\text{ONS}_2$ . Calculated %: C 63.14; H 3.39; N 4.91.

**5-Phenylthiazolidinedione-2,4-(I,  $\text{R}' = \text{C}_6\text{H}_5$ ,  $\text{R}'' = \text{R}''' = \text{H}$ ).** A mixture of 0.7 g of 5-phenylpseudothiohydantoin and 10 ml of concentrated hydrochloric acid were boiled for 8 hrs under reflux. The reaction mixture was evaporated to dryness; the residue was washed with water and dried. The yield of white crystalline material was 0.55 g (79.7%) with m.p. 125° (from alcohol). The literature data: M.p. 125-126° [5].

Found %: N 7.59.  $\text{C}_8\text{H}_7\text{O}_2\text{NS}$ . Calculated %: N 7.25.

Solutions containing 1 mg of the substance in 100 ml of ethanol were prepared for the spectrophotometric investigations. The measurements were carried out on a SF-4 spectrophotometer. The absorption spectrum of 3-phenyl-rhodanine was taken from [6].

#### SUMMARY

1. The introduction of phenyl groups into molecules of derivatives of thiozolidone-4 does not cause the appearance of a highly intense K-absorption band in the 350 to 425 m $\mu$  region.
2. The introduction of two or more phenyl groups into the molecule of a derivative of thiozolidone-4 leads to an increase in absorption intensity and also to a displacement of the absorption spectrum toward the long wave-length region.
3. One can obtain 3,5-diphenylrhodanine by the condensation of the ethyl ester of  $\alpha$ -chlorophenylacetic acid with potassium phenyldithiocarbamate.

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# ORIENTATION ON SUBSTITUTION IN THE AROMATIC SERIES

## IX. ON THE EQUILIBRIUM BETWEEN THE ISOMERS OF DICHLOROBENZENE

Yu. G. Erykalov and A. A. Spryskov

The Ivanov Chemico-Technological Institute

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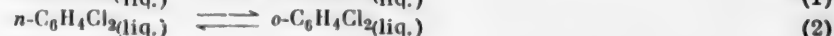
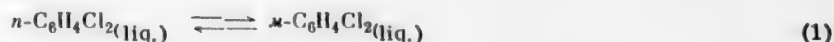
Original article submitted July 18, 1960

We have previously calculated from experimental data the equilibrium constants of the isomerization reaction of dichlorobenzene for a temperature of 160° [1]. The results of calculations of these same equilibrium constants at other temperatures are given below and also the results of calculations of the thermodynamic magnitudes which characterize the given process.

Starting from data on the heats of combustion and formation of the isomers of dichlorobenzene under standard conditions [2], and from the data of Narbutt [3] on the heat capacities of the isomers and the heat of fusion of p-dichlorobenzene, we calculated the heats of formation of the isomers

$$\left( \Delta H = \Delta H_0 + \int_{T_0}^T C_p dT \right)$$

and the change of enthalpy of the reactions



The enthalpy for reaction 1 increases from 1004 cal/mole at 100° to 1263 cal/mole at 200°, and for reaction 2 correspondingly from 1694 to 1953 cal/mole. The equations and the data of Narbutt for the calculation of the heat capacities of the dichlorobenzenes, are justified within the limits: Ortho, from -36 to +102°; meta, from -37 to +104°, para<sub>solid</sub>, from -78 to +52°; and para<sub>liquid</sub>, from +53 to +99°.

We used these equations for the calculations of heat capacities over a wider temperature interval (up to 200°), and this may introduce a small error into the calculations. Using our earlier values of the equilibrium constants of the corresponding reactions [1] and the values of the change of enthalpy, we calculated the equilibrium constants of reactions 1 and 2 for temperatures from 100 to 200  $\left( \lg K_x = \lg K + \frac{\Delta H_x (T_x - T)}{4.575 \cdot T_x \cdot T} \right)$ . The results of the calculations of the equilibrium constants, of the change of isobaric potential ( $\Delta Z = -4.575 T \lg K$ ), and of the entropy  $\left( \Delta S = \frac{\Delta H - \Delta Z}{T} \right)$  are given in Table 1.

For a comparison of the magnitudes of the change of entropy for reactions 1 and 2 with the corresponding statistical data [4], we calculated the entropy of vaporization of the isomers of dichlorobenzene at atmospheric pressure  $\left( \Delta S_{\text{vap.}} = \frac{\lambda_{\text{vap.}}}{T} \right)$  (Table 2), and the change of entropy for reactions 1 and 2 for the gas phase at a temperature of 180° (Table 3). The heats of vaporization of the isomers were calculated for this purpose from the data of [5] on the vapor tension of the dichlorobenzenes (Table 2).

Considering that we used the experimental data of different authors for the calculations, and considering also the possible errors in calculation by the methods of statistical thermodynamics, reasonably satisfactory agreement was found in the values cited in Table 3.

TABLE 1

Temperature	Para <sub>liquid</sub> $\rightleftharpoons$ meta <sub>liquid</sub>			Para <sub>liquid</sub> $\rightleftharpoons$ ortho <sub>liquid</sub>		
	K	$\Delta Z^\circ$	$\Delta S^\circ$	K	$\Delta Z^\circ$	$\Delta S^\circ$
120°	1.532	-0.33	3.4	0.419	0.68	2.6
160	1.735	-0.47	3.6	0.515	0.57	2.8
180	1.839	-0.55	3.8	0.566	0.51	3.0
200	1.947	-0.63	—	0.618	0.45	—

TABLE 2

Isomer	$\lambda_{\text{vap.}}$	$\Delta S_{\text{vap.}}$
Para	9885	22.1
Ortho	9935	21.9
Meta	9815	22.0

TABLE 3

$\Delta S$ of the reactions	
Para <sub>gas</sub> $\rightleftharpoons$ Meta <sub>gas</sub>	Para <sub>gas</sub> $\rightleftharpoons$ Ortho <sub>gas</sub>
3.7	2.8
2.2*	1.6*

\* Calculated from the data of [4].

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## CARBON SUBOXIDE AND SOME OF ITS REACTIONS

### XI. REACTION OF CARBON SUBOXIDE WITH 2-AMINOTHIAZOLE AND ITS DERIVATIVES

L. B. Dashkevich

Leningrad Institute of Pharmaceutical Chemistry

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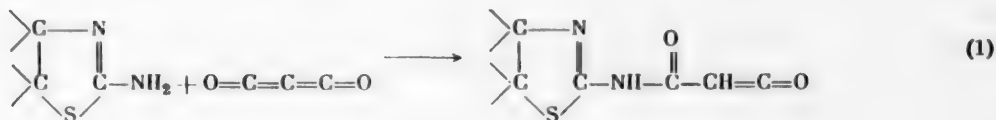
Original article submitted January 21, 1961

The reaction of carbon suboxide with substituted acyclic and carbocyclic monoamines has been investigated previously. However, in the described cases either only the N,N'-malonyl-bis-substituted amines and N-malonylamines, or polymeric products, were obtained [1-4]. This was explained by the fact that the indicated substituted amines reacted with carbon suboxide exclusively via their reactive amino group. Diamines with carbon suboxide give hexa- and macrocyclic systems [5]. The reaction of carbon suboxide with compounds, containing besides the amino group, other groups of approximately equivalent reactivity, has not been studied. The literature also fails to contain data on the reaction of carbon suboxide with imines.

In the present study our goal was to investigate the reaction of carbon suboxide with certain compounds, capable of amine-imine tautomerism, since it was postulated that the reactivity of a secondary amine group will be approximately equal to that of an imino group. In such case, the formation of the 4,6-dihydroxypyrimidine ring could be expected.

As is known, 2-aminothiazole and its 4,5-substituted derivatives can exist and react in two tautomeric forms, of which the imino form exhibits the more basic properties [6]. If the reaction of the amino tautomer with carbon suboxide should give N, N'-malonyl-bis-2-aminothiazoles, then the imino tautomer should obviously be capable of reacting to give the corresponding dihydroxypyrimidines.

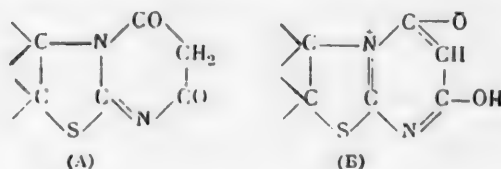
We established that 2-aminothiazoline (I), 2-aminothiazole (II), 2-amino-4-methylthiazole (III), 2-amino-4-phenylthiazole (IV), 2-aminobenzothiazole (V) and 2-amino-6-methylbenzothiazole (VI) react readily with carbon suboxide in the cold to yield compounds that represent the addition products of one molecule of amine to one molecule of  $C_3O_2$ . The possibility was not excluded that the reaction went in accordance with the scheme, characteristic for certain substituted amines [4, 7], and in the initial stage led to the formation of thiazolylcarbamoylethylmethylenes.



To prove that the compounds synthesized by us are dihydroxypyrimidothiazoles, we took the infrared spectra of the obtained compounds in the region of the intense absorption band of the NH group. In our opinion, the absence of this band indicates that the reaction products of carbon suboxide with aminothiazoles are dihydroxypyrimidothiazoles, since for the other possible cases the presence of the NH band is obligatory.

On the basis of the experimental data, the analogy with the general chemical properties of carbon suboxide and substituted aminothiazoles, and also the chemical and spectral analyses, we postulate that the reaction of  $C_3O_2$  with (I-VI) yields compounds of general formula A, and respectively: 2, 3-(dihydroxypyrimido)-thiazoline (VII),

2,3-(dihydroxypyrimido)thiazole (VIII), 4-methyl-2,3-(dihydroxypyrimido)thiazole (IX), 4-phenyl-2,3-(dihydroxypyrimido)thiazole (X), 2,3-(dihydroxypyrimido)benzothiazole (XI) and 6-methyl-2,3-(dihydroxypyrimido)benzothiazole (XII). The literature data concerning the structure peculiarities of the amido group in heterocyclic systems [8, 9] does not permit excluding the possibility of the existence of formula B with a bipolar ion.



The existence of keto-enol tautomerism in the dihydroxypyrimidine ring is highly probable. However, the problems of tautomerism should be the subject of a further detailed study.

Together with the dihydroxypyrimidothiazoles, a small amount of secondary high-melting compounds was always obtained from the reaction, the removal of which could be effected by repeated recrystallization. The latter is the reason for the comparatively low yields of purified products.

#### EXPERIMENTAL

Gaseous carbon suboxide [10, 11] was admitted into the reaction vessel directly from the pyrolysis furnace. In all of the experiments described below the reaction of  $C_3O_2$  with the aminothiazoles was run at room temperature and a 150% excess of  $C_3O_2$  was used.

(I), m. p. 84-85°C (from benzene) [12]; (II) was obtained by the procedure given in [13], but instead of  $\alpha$ ,  $\beta$ -dichloroethyl butyl ether we used  $\alpha$ ,  $\beta$ -dibromoethyl butyl ether; m.p. 89-90°C, yield 65%; (III), m.p. 44-45°C [14]; (IV), m.p. 147°C (from benzene) [15]; (V), m.p. 128-129°C (from water [16]; (VI), m.p. 135-136°C [17].

**Reaction of Carbon Suboxide with 2-Aminothiazoline (I).** A solution of 1.0 g of (I) in 40 ml of absolute ether was placed in a 100-ml flask and a steady stream of gaseous carbon suboxide was passed through the mixture. Soon a finely crystalline precipitate began to deposit. The reaction was ended in 1 hr. After standing for a short time, the precipitate was filtered, followed by several recrystallizations from methanol. (VII) is moderately soluble in acetone, alcohol, and hot water, difficultly soluble in ether, and soluble in dilute alkalis; it does not decolorize bromine in carbon tetrachloride solution, cannot be iodomethylated, and fails to form picrates or picrolonates.

**Reaction of Carbon Suboxide with Amines (II-VI).** The reaction was run in the same manner as described above. The solubility and other mentioned properties of compounds (VIII-XII) are approximately the same as those of (VII). The properties of the obtained compounds are given in the table.

Compound	Yield in %	M. p.	Empirical formula	% N		% S		M	
				Found	Calcd	Found	Calcd	Found	Calcd
VII	72	240-241° (methanol)	$C_6H_6O_2N_2S$	16.25	16.45	18.5	18.96	173	170.12
(VIII)	53	241-242° (methanol)	$C_6H_4O_2N_2S$	16.46	16.65	18.7	19.06	165	168.12
(IX)	58	210-211° (methanol)	$C_7H_6O_2N_2S$	15.42	15.37	17.8	17.74	181	182.13
(X)	55	209-210° (dichloroethane)	$C_{12}H_8O_2N_2S$	11.58	11.47	13.0	13.12	241	244.19
(XI)	62	239-240° (benzene)	$C_{10}H_6O_2N_2S$	12.78	12.83	14.5	14.69	222	218.16
(XII)	65	241-242° (benzene)	$C_{11}H_8O_2N_2S$	12.06	12.05	13.9	13.80	229	232.17



The spectra were taken using an IRS-12 infrared spectrophotometer and a LiF prism. Since the compounds were difficultly soluble in carbon tetrachloride, the samples for the spectra were prepared as powders (Freon oil was used as the immersion liquid). The absorption bands, corresponding to the stretching vibration of the NH group (3200-3450  $\text{cm}^{-1}$  region), are absent in the spectra of the obtained products (VII-XII).

#### SUMMARY

1. The reaction of carbon suboxide in the cold with 2-aminothiazole and some of its derivatives leads to the formation of the corresponding dihydroxypyrimidothiazoles.

2. It is possible to assume that in addition to the aminothiazoles, some other nitrogen-containing heterocyclic compounds, capable of amine-imine tautomerism, will react with carbon suboxide to give compounds containing dihydroxypyrimidine rings.

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# SYNTHESIS OF SUBSTITUTED 1, 4-DIPHENYLTHIOSEMICARBAZIDE DERIVATIVES

P. S. Pel'kis and M. Z. Peretyazhko

Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR

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In recent years a large number of various substituted 1,4-diphenylthiosemicarbazide derivatives have been synthesized [1-3], mainly for the purpose of studying their physiological activity, although the sulfonamido and carboxy derivatives have received little study.

Recently some Rumanian investigators have shown that in the case of thiocarbanilide derivatives the presence of a methyl group in the p-position leads to an enhancement in the antitubercular properties of the compounds [4]. In connection with this it seemed of interest to synthesize and study a number of unsymmetrically substituted 1, 4-diphenylthiosemicarbazide derivatives containing a methyl group in the p-position.

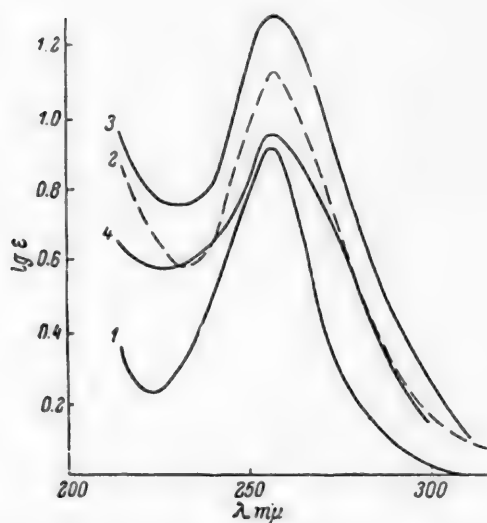
In a previous paper [5] we described the synthesis of several substituted 1,4-diphenylthiosemicarbazide derivatives. In the present study the unsymmetrically substituted 1, 4-diphenylthiosemicarbazide derivatives were synthesized from arylhydrazines and aryl isothiocyanates:



The starting aryl isothiocyanates were obtained from the corresponding amines and thiophosgene in hydrochloric acid medium [6].

The substituted 1, 4-diphenylthiosemicarbazide derivatives synthesized by us are listed in the table.

From the data in the table it can be seen that the substituted 1,4-diphenylthiosemicarbazide derivatives are crystalline compounds with high melting points. They are soluble in aqueous alkali and slightly soluble in organic solvents. They were purified by reprecipitation with dilute acids from alkaline solution, followed by recrystallization from aqueous alcohol or alcohol-acetone solutions. The ultraviolet absorption curves of several substituted 1,4-diphenylthiosemicarbazide derivatives are shown in the Figure. An SF-4 spectrophotometer was used to take the measurements. As can be seen, the substituted 1, 4-diphenylthiosemicarbazide derivatives are characterized by absorption curves with a maximum in the 250-260 mμ region. It should be mentioned that the position of the absorption maxima is apparently quite independent of the electronic nature of the substituents in the phenyl groups of the thiosemicarbazide and is determined by the thiosemicarbazide grouping.



Absorption spectra of alcohol solutions of substituted 1, 4-diphenylthiosemicarbazide derivatives. 1) 1-(p-Sulfamoylphenyl)thiosemicarbazide; 2) 1-(p-sulfamoylphenyl)-4-(p-tolyl)thiosemicarbazide; 3) 1-(p-sulfamoylphenyl)-4-(phenethyl)thiosemicarbazide; 4) 1-(p-sulfamoylphenyl)-4-(p-chlorophenyl)thiosemicarbazide. The concentration for curves 1 and 3 was  $3.3 \times 10^{-5}$  M, for curve 2 it was  $6.6 \times 10^{-5}$  M, and for curve 4 it was  $2.6 \times 10^{-5}$  M.

Substituted 1,4-Diphenylthiosemicarbazide Derivatives, RNHNHCSNHR'

No. of compound	R	R'	M. p.	Yield, in %	Empirical formula	% S	
						Found	Calcd.
I	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	p-HOOC <sub>6</sub> H <sub>4</sub>	154° (decompn.)	73	C <sub>15</sub> H <sub>15</sub> O <sub>2</sub> N <sub>3</sub> S	10.56, 10.67	10.83
II		m-OH <sub>2</sub> p-HOOC <sub>6</sub> H <sub>3</sub>	201	62	C <sub>15</sub> H <sub>15</sub> O <sub>3</sub> N <sub>3</sub> S	9.99, 9.95	10.09
III		p-H <sub>2</sub> NSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	290	73	C <sub>14</sub> H <sub>14</sub> O <sub>2</sub> N <sub>4</sub> S <sub>2</sub>	19.27, 19.48	19.04
IV		p-NaO <sub>3</sub> SC <sub>6</sub> H <sub>4</sub>	290 (decompn.)	72	C <sub>14</sub> H <sub>14</sub> O <sub>3</sub> N <sub>3</sub> S <sub>2</sub> Na	17.82, 17.91	17.82
V		p-H <sub>2</sub> NCOHNSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	182	55	C <sub>15</sub> H <sub>17</sub> O <sub>3</sub> N <sub>3</sub> S <sub>2</sub>	16.72, 16.55	16.88
VI	p-NH <sub>2</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	o-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	188	88	C <sub>14</sub> H <sub>18</sub> O <sub>2</sub> N <sub>4</sub> S <sub>2</sub>	18.95, 18.94	19.04
VII		p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	202	94	C <sub>14</sub> H <sub>16</sub> O <sub>2</sub> N <sub>4</sub> S <sub>2</sub>	19.13, 19.20	19.04
VIII		o,p-(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	178	93	C <sub>15</sub> H <sub>18</sub> O <sub>2</sub> N <sub>4</sub> S <sub>2</sub>	18.31, 18.36	18.28
IX		o-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	212	79	C <sub>14</sub> H <sub>16</sub> O <sub>3</sub> N <sub>4</sub> S <sub>2</sub>	18.41, 18.55	18.18
X		p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	231	85	C <sub>14</sub> H <sub>16</sub> O <sub>3</sub> N <sub>4</sub> S <sub>2</sub>	18.26, 18.33	18.18
XI		p-C <sub>2</sub> H <sub>5</sub> OC <sub>6</sub> H <sub>4</sub>	221-222 (decompn.)	42	C <sub>15</sub> H <sub>18</sub> O <sub>3</sub> N <sub>4</sub> S <sub>2</sub>	17.81, 18.01	17.48
XII		p-n-C <sub>4</sub> H <sub>9</sub> OC <sub>6</sub> H <sub>4</sub>	211-212 (decompn.)	95	C <sub>17</sub> H <sub>22</sub> O <sub>3</sub> N <sub>4</sub> S <sub>2</sub>	16.53, 16.58	16.24
XIII		p-ClC <sub>6</sub> H <sub>4</sub>	200-202 (decompn.)	74	C <sub>13</sub> H <sub>13</sub> O <sub>2</sub> N <sub>4</sub> S <sub>2</sub> Cl*	17.83, 17.84	17.95
XIV		p-CH <sub>3</sub> COC <sub>6</sub> H <sub>4</sub>	194-195 (decompn.)	51	C <sub>15</sub> H <sub>16</sub> O <sub>3</sub> N <sub>4</sub> S <sub>2</sub>	17.28, 17.30	17.58
XV		p-CH <sub>3</sub> COC <sub>6</sub> H <sub>4</sub>	> 280	62	C <sub>16</sub> H <sub>18</sub> O <sub>3</sub> N <sub>3</sub> S	9.86, 10.00	9.72
XVI	p-HOOC <sub>6</sub> H <sub>4</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	188-190 (decompn.)	74	C <sub>15</sub> H <sub>15</sub> O <sub>2</sub> N <sub>3</sub> S	10.05, 10.22	10.63
XVII		C <sub>6</sub> H <sub>5</sub>	213	85	C <sub>14</sub> H <sub>13</sub> O <sub>2</sub> N <sub>3</sub> S	11.32, 11.40	11.15

\* Found %: C 43.52; H 3.70; N 15.65; Cl 9.64. Calculated %: C 43.75; H 3.64; N 15.70; Cl 9.94

According to the data of the Ukrainian Tuberculosis Institute of the Ministry of Public Health of the Ukrainian SSR (Kiev), the 1,4-diphenylthiosemicarbazide derivatives listed in the table exhibit tuberculostatic activity at dilutions of 1:50,000 to 1:500,000.

#### EXPERIMENTAL

p-Sulfamoylphenylhydrazine [7]. A suspension of 5.6 g of white streptocide (sulfanilamide) in 25 ml of 15% hydrochloric acid was cooled and then diazotized with a solution of 2.3 g of sodium nitrite in 6 ml of water. Toward the end of the diazotization the entire mixture turned to a dark orange solution. Then the diazonium salt solution was added to a solution of sodium sulfite (19 g in 100 ml of water) at 0°, after which the entire mixture was heated on the boiling water bath for 1 hr, 15 ml of hydrochloric acid was added, and the solution was heated for another 3 hr. At the end of this time another 40 ml of hydrochloric acid was added and the whole was allowed to stand overnight. The next day the hydrazine salt, obtained as lustrous orange plates, was filtered and washed with a little alcohol. The hydrochloride was converted to the free base by neutralization with 10% NaOH solution. M.p. 156-157°C. Yield 2.5 g (45%).

p-Ureidosulfonylphenyl mustard oil. With vigorous stirring, a suspension of 31.5 g of thiophosgene in water (10 volume parts) was treated at 15°C with a solution of 20 g of urosulfan (sulfanilylurea) in chloroform (5 volume parts). After stirring for 5 hr, the chloroform layer was separated and dried over calcium chloride. The solvent and excess thiophosgene were distilled off on the water bath. The residue was a colorless crystalline product with m.p. 174°C. Yield 32 g (85%).

1-(p-sulfamoylphenyl)-4-(p-acetophenyl)thiosemicarbazide (XIV). A mixture of 1.0 g of p-sulfamoylphenylhydrazine and 1.0 g of acetophenyl isothiocyanate in 100 ml of methanol was stirred for 5 hr. The entire mixture went into solution. A yellow precipitate was obtained after removing most of the methanol. The precipitate was filtered and recrystallized twice from alcohol. M. p. 194-195°C (decompn.). Yield 1.0 g (52%).

The substituted 1,4-diphenylthiosemicarbazide derivatives listed in the table were obtained from the corresponding phenylhydrazine derivatives and phenyl mustard oil derivatives under analogous conditions. The end of the condensation was determined by the absence of a positive test for the hydrazine using sodium nitroprusside and formaldehyde in alkaline medium [8].

#### SUMMARY

Seventeen new 1,4-diphenylthiosemicarbazide derivatives were synthesized and the absorption spectra of some of them were measured.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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## THIOSULFONIC ACIDS

### VII. ARYL ESTERS OF BENZENETHIOSULFONIC ACID AND ITS DERIVATIVES

B. G. Boldyrev and L. M. Khovalko

Lwow Polytechnic Institute

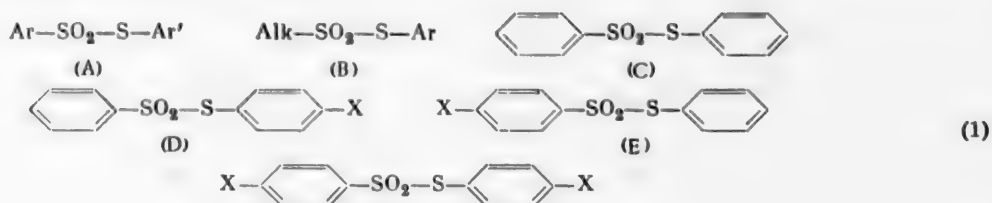
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 11,

pp. 3729-3734, November, 1961

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Among the esters of thiosulfonic acids the most completely studied are the aryl esters (A) of arenethiosulfonic acids, but up to now information regarding their antibacterial activity is lacking in the literature. At the same time, in their structure these compounds resemble the aryl esters (B) of alkanethiosulfonic acids, which exhibit a high fungicidal activity [1], and consequently can be of practical interest.

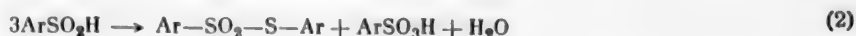
Our objective was to prepare some aryl esters of benzenethiosulfonic acid and its derivatives of structure (C-F) and make a study of their antimicrobial properties.



The compounds that we decided to synthesize made it possible to elucidate the effect of the structure of the esters on their antimicrobial activity, and also to use these compounds for further physicochemical studies, the results of which will be reported later.

The obtained aryl esters of arenethiosulfonic acids are listed in the table.

The esters of symmetrical structure (C) and (F) were prepared by a known procedure [2]—the dismutation of sulfinic acids when they are heated in glacial acetic acid.



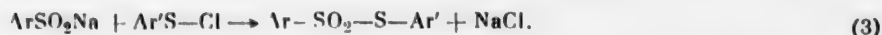
We attempted to prepare the benzyl ester of phenylmethanethiosulfonic acid (XVII) by the dismutation of phenylmethanesulfinic acid, and also by the oxidation of dibenzyl disulfide, under the conditions described by the Italian investigators [3,4]. However, it proved that under these conditions the dibenzyl disulfide undergoes more profound oxidation and gives a substantial amount of benzaldehyde; here the yield of the ester was very small and it proved almost impossible to isolate it in a pure state.

Phenylmethanesulfinic acid also gives hardly any ester when the dismutation reaction is run, since it decomposes with ease to give benzaldehyde and sulfur dioxide.

We obtained better results when dibenzyl disulfide was oxidized with 30% hydrogen peroxide in glacial acetic acid, although the formation of a substantial amount of benzaldehyde was also observed under these conditions, and the total yield of the ester was only 13%.

The p-aminophenyl ester of thiosulfanilic acid (XVI) was prepared by the reaction of its diacetyl derivative with concentrated hydrochloric acid.

Esters (D) and (E) of unsymmetrical structure were obtained by reacting the appropriate sodium sulfinates with the sulfenyl chlorides:



The arenesulfenyl chlorides were obtained in the usual manner [5-7]—by the reaction of chlorine with solutions of the thiophenols or disulfides in either absolute carbon tetrachloride or ether. In this connection the carbon tetrachloride solutions of the thiophenols were added, with cooling, to an equimolar amount of chlorine dissolved in carbon tetrachloride, after which the solvent was vacuum-distilled, while the residue, representing the sulfenyl chloride, was either used as such for the syntheses, or was subjected to further purification by vacuum-distillation. In this manner, benzene- and p-chlorobenzenesulfenyl chlorides were prepared in a pure state; p-methoxybenzenesulfenyl chloride was obtained in a similar manner as a reddish-brown liquid, which failed to distill at a vacuum of  $10^{-2}$  mm. For this reason it was used without further purification. Attempts to prepare p-acetamidobenzenesulfenyl chloride by the same procedure, and also by the chlorination of bis(p-acetamidophenyl) disulfide, proved unsuccessful: the yield of the sulfenyl chloride was very small, and the obtained product was highly contaminated with the starting disulfide, for which reason the final esters, which we attempted to prepare using this crude sulfenyl chloride, were obtained slightly contaminated, and their yields were extremely low.

In view of this, to synthesize the p-acetamidophenyl ester of benzenethiosulfonic acid (V) we used p-acetamidobenzenesulfenyl bromide, which was obtained in known manner [8] by the bromination of the same disulfide. However, also in this case the disulfide reacted only partially and the yield of the ester was very small. When the reaction was run, a substantial amount of unchanged disulfide was recovered from the reaction mixture.

Esters (VI) and (XI) were obtained from their acetyl derivatives by treatment of the latter with concd. hydrochloric acid. The hydrochlorides of these compounds proved to be very unstable and they hydrolyzed with ease when dissolved in water; in this connection the hydrochloride of the p-aminophenyl ester of benzenethiosulfonic acid was hydrolyzed to the free base of the ester, which was obtained as a precipitate, while in the case of dissolving the hydrochloride of the phenyl ester of thiosulfanilic acid in water not only hydrolysis of the salt occurred, but also a further destruction of the ester. The latter apparently went in a manner that is customary for compounds of this type [9], since one of the decomposition products of the ester was diphenyl disulfide, which we were able to isolate. For this reason, the hydrochloride was converted to the free base by treating the hydrochloride with dry ammonia gas in absolute carbon tetrachloride medium.

Most of the thiosulfonic acid esters listed in the table are colorless crystalline compounds; some of them have a straw or pale yellow color (compounds IV, VI, IX, XV, XVI), while ester (XIV) has a distinct yellow color. Compound (V) is nearly colorless when first prepared, but when kept in the light it very rapidly assumes a yellow color, which is lost just as rapidly when the compound is placed in the dark.

All of the compounds are very slightly soluble in water, and in contrast to other thiosulfonic acid esters, are much more difficultly soluble than the latter in organic solvents.

A study of the antimicrobial activity of the aromatic esters of arenethiosulfonic acids, carried out in the Institute of Microbiology of the Academy of Sciences of the Ukrainian SSR,\* revealed that these compounds, in contrast to the alkyl esters of thiosulfonic acids, are ineffective against gram-negative bacteria, similar to the situation that prevails for the aromatic esters of alkanethiosulfonic acids [18]. As a result, this is apparently a specific property of all aromatic esters of thiosulfonic acids.

It should be mentioned that with respect to other kinds of bacteria, and especially toward fungi, the aromatic esters of arenethiosulfonic acids are inferior to the alkyl esters, especially the esters of symmetrical structure (XII–XVII). The greatest activity toward all of the investigated kinds of bacteria and fungi was displayed by the phenyl ester of benzenethiosulfonic acid (I); the benzyl ester of phenylmethanethiosulfonic acid (XVII) lacks antimicrobial activity and is practically devoid of fungicidal action against the same bacteria and fungi.

In the case of phytopathogenic fungi, the same esters exhibit a much greater activity, and some of them are equal to captan and even superior to zineb in their action when compared at the same concentration under laboratory conditions [1].

\* We wish to thank V. G. Drobot'ko, B. E. Aizenman, S. I. Zelepukhe, and coworkers for making a study of the antimicrobial activity of these compounds.



Aryl Esters of Benzenethiosulfonic Acid and Its Derivatives Ar-SO<sub>2</sub>-S-Ar'

No. of compound	Ar	Ar'	M. p.	Empirical formula	% S		Yield, in %	Literature reference
					Found	Calcd.		
(I)	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	44°	C <sub>12</sub> H <sub>10</sub> O <sub>2</sub> S <sub>2</sub>	25.60	25.62	28.4	[10]
(II)	C <sub>6</sub> H <sub>5</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	68—69	C <sub>12</sub> H <sub>9</sub> O <sub>2</sub> S <sub>2</sub> Cl	22.68	22.52	40.0	[11]
(III)	C <sub>6</sub> H <sub>5</sub>	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	58	C <sub>13</sub> H <sub>12</sub> O <sub>2</sub> S <sub>2</sub>	23.10	22.88	35.5	—
(IV)	C <sub>6</sub> H <sub>5</sub>	p-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	106—107	C <sub>12</sub> H <sub>9</sub> O <sub>4</sub> NS <sub>2</sub>	21.83, 21.89	21.72	34.1	[11]
(V)	C <sub>6</sub> H <sub>5</sub>	p-CH <sub>3</sub> CONHC <sub>6</sub> H <sub>4</sub>	163—164	C <sub>14</sub> H <sub>13</sub> O <sub>2</sub> NS <sub>2</sub>	20.90	20.86	5.5	—
(VI)	C <sub>6</sub> H <sub>5</sub>	p-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	131—132	C <sub>12</sub> H <sub>11</sub> O <sub>2</sub> NS <sub>2</sub>	24.33	24.17	60.6	—
(VII)	p-ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	82	C <sub>12</sub> H <sub>9</sub> O <sub>2</sub> S <sub>2</sub> Cl	22.52	22.52	54.7	[11]
(VIII)	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	55	C <sub>13</sub> H <sub>12</sub> O <sub>2</sub> S <sub>2</sub>	23.06	22.88	48.0	—
(IX)	p-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	154—155	C <sub>12</sub> H <sub>9</sub> O <sub>4</sub> NS <sub>2</sub>	21.72, 21.86	21.72	40.0	[11]
(X)	p-CH <sub>3</sub> CONHC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	154—155	C <sub>14</sub> H <sub>13</sub> O <sub>2</sub> NS <sub>2</sub>	21.06	20.86	53.9	—
(XI)	p-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	144—145	C <sub>12</sub> H <sub>11</sub> O <sub>2</sub> NS <sub>2</sub>	24.13	24.17	55.0	—
(XII)	p-ClC <sub>6</sub> H <sub>4</sub>	p-ClC <sub>6</sub> H <sub>4</sub>	137—138	C <sub>12</sub> H <sub>9</sub> O <sub>2</sub> S <sub>2</sub> Cl <sub>2</sub>	20.09	20.09	90.9	[12, 13]
(XIII)	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	88	C <sub>14</sub> H <sub>14</sub> O <sub>4</sub> S <sub>2</sub>	20.84	20.66	80.0	[12, 13]
(XIV)	p-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	p-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	182—183	C <sub>12</sub> H <sub>9</sub> O <sub>4</sub> N <sub>2</sub> S <sub>2</sub>	18.70	18.84	27.2	[14, 15]
(XV)	p-CH <sub>3</sub> CONHC <sub>6</sub> H <sub>4</sub>	p-CH <sub>3</sub> CONHC <sub>6</sub> H <sub>4</sub>	222—223	C <sub>16</sub> H <sub>16</sub> O <sub>4</sub> N <sub>2</sub> S <sub>2</sub>	17.35, 17.36	17.60	61.4	[16]
(XVI)	p-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	p-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	185—186	C <sub>12</sub> H <sub>12</sub> O <sub>2</sub> N <sub>2</sub> S <sub>2</sub>	23.07	22.87	56.0	[16]
(XVII)	C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	108	C <sub>14</sub> H <sub>14</sub> O <sub>2</sub> S <sub>2</sub>	23.10, 23.14	23.04	13.3	[17, 3]

## EXPERIMENTAL\*

The starting products for all of the syntheses were the sulfonyl chlorides, having constants corresponding to the literature data [19].

Reduction of the acid chlorides with either sodium sulfite or with zinc dust [20] gave respectively, either sulfonic acids and their salts, or thiophenols. The latter were converted to the sulfonyl chlorides by reaction with chlorine, using the procedures described in [5-7].

The previously described techniques of synthesizing the aromatic esters of arenethiosulfonic acids were refined in the present study.

**p-Acetamidophenyl Ester of Benzenethiosulfonic Acid (V).** Sodium benzenesulfinate was prepared by the reduction of benzenesulfonyl chloride with sodium sulfite [20], while the sulfonyl bromide was prepared by the bromination of bis (p-acetamidophenyl) disulfide [8]. The latter, in turn, was obtained from p-nitrochlorobenzene by the procedure given in [21], with subsequent acylation of the reaction product.

Even under the optimum conditions (reaction temperature  $-5^{\circ}\text{C}$ ), the yield of p-acetamidobenzenesulfonyl bromide was very small; two thirds of the starting disulfide was recovered unchanged. If the reaction of the disulfide with bromine is run at an elevated temperature, or if the reaction time is increased, then the yield of the sulfonyl bromide, judging by the final product, is not increased.

With stirring and cooling to  $-5^{\circ}\text{C}$ , a solution of 9.65 g of bromine in 20 ml of absolute  $\text{CCl}_4$  was added gradually to a suspension of 20.0 g of bis (p-acetamidophenyl) disulfide in 250 ml of absolute  $\text{CCl}_4$ ; after this the reaction mass was kept at the same temperature for 2 hr, and then the precipitate was filtered rapidly, washed with carbon tetrachloride, and added to a suspension of 21.2 g of anhydrous sodium benzenesulfinate in 250 ml of absolute toluene. The reaction mass was heated to the boil, and then with stirring was heated under reflux for 5 hr. Then the mixture was filtered and the filtrate on cooling deposited the ester; removal of the solvent by distillation gave an additional amount of the ester. The total yield was 5.5 g, m.p.  $152-153^{\circ}\text{C}$ . After three recrystallizations from benzene, and then from 50% alcohol, we obtained 2.2 g of the p-acetamidophenyl ester of benzenethiosulfonic acid as a straw-yellow crystalline product with a constant melting point of  $163-164^{\circ}\text{C}$ .

We were able to obtain 13.7 g of the starting disulfide from the precipitate, isolated in the filtration of the principal reaction mass.

**p-Aminophenyl ester of benzenethiosulfonic acid (VI).** A mixture of 5.4 g of the p-acetamidophenyl ester of benzenethiosulfonic acid and 10 ml of concd. hydrochloric acid (d 1.19) was heated under reflux; within 10-15 min the precipitate dissolved completely and the obtained solution on cooling deposited the product as a viscous yellow oil, which apparently was the impure hydrochloride of the ester.\*\* The crystalline ester began to deposit gradually when this oil was dissolved in water. To obtain complete separation of the ester, the oily product was poured rapidly into water, the obtained solution was shaken with activated carbon, filtered, and the filtrate was treated with 5% ammonia solution until weakly acid to Congo. The thus obtained slightly yellow precipitate was filtered, washed with water, and then recrystallized from 50% alcohol to a constant melting point of  $131-132^{\circ}\text{C}$ . The yield of the ester was 2.8 g.

**Phenyl Ester of Acetylthiosulfanilic Acid (X).** This ester was synthesized in the same manner as (V), by the reaction of the sodium salt of p-acetamidobenzenesulfonic acid with benzenesulfonyl chloride in absolute toluene medium. The benzenesulfonyl chloride was prepared from thiophenol by the procedure given in [22]. It was purified by vacuum-distillation and had b.p.  $73-75^{\circ}\text{C}$  at 9 mm.

In this connection, from 30.8 g of the sodium sulfinate and 17.3 g of benzenesulfonyl chloride in 300 ml of absolute toluene, with a heating time of 3 hr, we obtained 19.8 g of the ester (53.8%, based on the sulfonyl chloride) with a constant melting point of  $154-155^{\circ}\text{C}$ .

**Phenyl Ester of Thiosulfanilic Acid (XI).** Six grams of the phenyl ester of acetylthiosulfanilic acid was suspended in 11.0 ml of concd. hydrochloric acid, heated to the boil with stirring, and then held at this temperature until all of the precipitate had dissolved (15-20 min). When the solution was cooled the hydrochloride of the ester came out rapidly as plates, which were filtered, washed with hydrochloric acid, and dried in a vacuum-desiccator.

\* With the assistance of S. A. Zubarev.

\*\* The pure hydrochloride was obtained as a colorless crystalline product with m.p.  $171-172^{\circ}\text{C}$  (decompn.) by treating a solution of the free base of the ester in absolute benzene with gaseous hydrogen chloride.

The amount of product obtained was 5.2 g, m.p. 153°C. The hydrochloride of the ester is extremely unstable: even when dissolved in water the hydrochloride undergoes hydrolysis, and then also the ester. For this reason, neutralization of the hydrochloride and isolation of the free base was carried out in anhydrous medium. With stirring, a stream of dry ammonia gas was passed through a suspension of 5.2 g of the hydrochloride in 80 ml of absolute carbon tetrachloride until the temperature of the suspension failed to rise, which occurred at the start of reaction. Then the precipitate was filtered, washed with carbon tetrachloride, then with water, and after drying, the material was recrystallized from a 1:1 mixture of benzene and carbon tetrachloride, since the ester is soluble in benzene, alcohol, acetone or chloroform even at room temperature, while it is insoluble in carbon tetrachloride even when heated. The yield of pure product with m.p. 144–145°C was 2.5 g.

p-Chlorophenyl ester of p-chlorobenzenethiosulfonic acid (XII). This ester was obtained by the dismutation of p-chlorobenzenesulfinic acid in glacial acetic acid. In all cases the purity of the starting sulfinic acid exerts an important effect on the yields and quality of the esters: a high purity sulfinic acid assures obtaining the ester with the melting point given in the literature, not requiring further purification.

A suspension of 15.0 g of dry p-chlorobenzenesulfinic acid, m.p. 97–98°C, in 30 ml of glacial acetic acid was heated under reflux on the boiling water bath for 1 hour. The reaction solution was then filtered, cooled, and the obtained precipitate of the ester was filtered, washed with warm water to remove traces of the sulfonic acid, and dried in a vacuum-desiccator. The product had m.p. 137–138°C, which agrees with the literature [13], and did not require further purification. The yield of the ester was 7.0 g.

Benzyl Ester of Phenylmethanethiosulfonic Acid (XVII). Into a three-necked flask, fitted with a reflux condenser, thermometer and a stirrer, were charged 4.0 g of pure dry dibenzyl disulfide with m.p. 70–71°C, 40 ml of glacial acetic acid and 2.5 ml of 30% hydrogen peroxide. The mixture was heated to 70°C in 1 hr, and then kept at this temperature for another 30 min. After cooling, the reaction mass was treated with a little water and the obtained benzaldehyde was separated, while the solution was kept in the cold until the benzyl ester of phenylmethanethiosulfonic acid came out as a precipitate. This precipitate was filtered and washed with water, while the filtrate was again diluted with water and the isolation of the ester was repeated. The obtained ester was washed twice with alcohol to remove traces of benzaldehyde, and then was recrystallized 5 times from alcohol in the presence of carbon until a product with m.p. 108°C was obtained. The benzaldehyde, formed in the oxidation, became thick on long standing, in which connection it deposited the same ester and was converted to a thick, viscous mass. The mass was filtered, and the precipitate was washed with water and then with alcohol, followed by repeated recrystallization from alcohol in the presence of carbon. The total yield of the pure product was 0.6 g.

#### SUMMARY

1. Seventeen aromatic esters of arenethiosulfonic acids were synthesized, including 6 new compounds; the known methods for their preparation were refined.
2. A brief characterization of the antimicrobial activity of these compounds was presented.

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# SYNTHESIS AND PROPERTIES OF TRIALKYL(TRIARYL)- (p-BROMOPHENOXY)SILANES

## II. TRIAMYL-, TRIHEXYL- AND TRIPHENYL-(p-BROMOPHENOXY)SILANES

G. V. Golodnikov and G. S. Afanas'eva

Leningrad State University

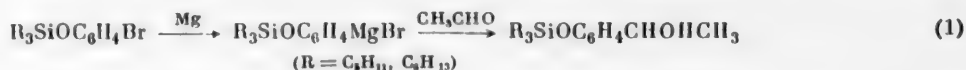
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Previously we had investigated the properties and reactions of the first three members in the series of silicon-containing bromides of general formula  $R_3SiOC_6H_4Br$  [1]. In particular, we were able to synthesize the secondary organosilicon alcohol by reacting acetaldehyde with the Grignard compound obtained from the bromide where  $R = C_3H_7$ .

Our objective in the present study was to synthesize and study the properties of the triamyl-, trihexyl- and triphenyl- (p-bromophenoxy)silanes. These compounds, previously unknown, were obtained in yields of 73 to 94% by the catalytic dehydrocondensation [2] of the trialkylsilanes with p-bromophenol. The triamyl- and trihexyl- (p-bromophenoxy)silanes are colorless liquids, while triphenyl-(p-bromophenoxy)silane is a solid. The first two bromides were used in subsequent work to obtain the secondary alcohols in accordance with the scheme:



It should be mentioned that the bromides did not react with magnesium under the usual conditions. However, the addition of ethyl bromide to the reaction mixture in a molar ratio of 1:1 to the silicon-containing bromide facilitated the successful formation of the organomagnesium compound. The carbinolates obtained from the condensation of the Grignard reagents with acetaldehyde were decomposed with pure water (in order to avoid hydrolysis at the Si-O-C bond). The yield of methyl (p-triamylsiloxylphenyl) carbinol was 47%, and that of methyl (p-trihexylsiloxylphenyl) carbinol was 36%. Besides the alcohols, in both cases the reaction products were found to contain the trialkylphenoxysilanes, which were formed by the decomposition of the unreacted Grignard reagent with water, and also a small amount of tar.



The yields of  $R_3SiOC_6H_5$  were: 15% when  $R = C_4H_9$ , and 9% when  $R = C_6H_{13}$ .

The obtained secondary alcohols are liquids, which can be distilled in vacuo without decomposition. The absence of trialkylsilanols and hexaalkyldisiloxanes in the reaction products testifies to the hydrolytic stability of the Si-O-C linkage in the alcohols. This must be due to the shielding action of the amyl and hexyl groups, linked to the silicon atom. The molecular weights, the silicon content and the found molecular refraction values are in good agreement with those calculated for the two alcohols. The alcohols react with metallic sodium with the evolution of hydrogen. The obtained infrared spectra of the alcohols show absorption maxima at  $3380\text{ cm}^{-1}$  ( $R = C_6H_{13}$ ) and  $3400\text{ cm}^{-1}$  ( $R = C_4H_9$ ). According to the literature [3], the band, corresponding to the stretch vibrations of the OH group when intermolecular hydrogen bonds are present, lies in the  $3450\text{--}3200\text{ cm}^{-1}$  region. The properties of the alcohols are listed in Table 1 (for comparison, we have also given the properties of the previously obtained alcohol where  $R = C_3H_7$ ).

Table 1

Properties of Methyl (p-Trialkylsiloxyphenyl) carbinols,  $p\text{-R}_3\text{SiOC}_6\text{H}_4\text{CHOHCH}_3$ 

R	B.p. (pressure in mm)	$d_4^{20}$	$n_D^{20}$	M		$M R_p$		Formula		% Si	
				Found	Calcd.	Found	Calcd.			Found	Calcd.
$\text{C}_3\text{H}_7^{[1]}$	181—183°(15)	1.0345	1.5088	294.0	294.5	85.99	89.21	$\text{C}_{17}\text{H}_{30}\text{O}_2\text{Si}$		9.65	9.51
$\text{C}_6\text{H}_{11}$	208—216°(5)	0.9589	1.4885	369.9, 351.8	378.6	114.9	115.5	$\text{C}_{23}\text{H}_{42}\text{O}_2\text{Si}$		7.33, 7.21	7.41
$\text{C}_8\text{H}_{13}$	233—238°(6)	0.9654	1.4990	420.6, 423.5	420.7	127.3	129.5	$\text{C}_{28}\text{H}_{48}\text{O}_2\text{Si}$		6.58, 6.51	6.68

Table 2

Trialkyl (triaryl)-(p-bromophenoxy)silanes,  $\text{R}_3\text{SiOC}_6\text{H}_4\text{Br-p}$ 

R	B.p. (pressure in mm)	$d_4^{20}$	$n_D^{20}$	M		$M R_p$		Formula	% Si		% Br		Reaction time, hr.	Yield, %
				Found	Calcd.	Found	Calcd.		Found	Calcd.	Found	Calcd.		
$\text{C}_3\text{H}_7$	218°(7)	1.0560	1.4952	400 407	413	114.2 114.0	114.0	$\text{C}_{21}\text{H}_{37}\text{OSiBr}$	6.90 6.82	6.79	19.20 19.20	19.30	1.5	94.0
$\text{C}_6\text{H}_{13}$	221 (2)	1.0300	1.4939	433 435	455	128.7 127.9	127.9	$\text{C}_{24}\text{H}_{43}\text{OSiBr}$	6.27 6.21	6.16	18.1	17.5	1.5	80.0
$\text{C}_8\text{H}_5$	270—274°(5)	—	—	—	—	—	—	$\text{C}_{24}\text{H}_{19}\text{OSiBr}$	6.74 6.75	6.52	18.06 18.70	18.60	30	73.3



## EXPERIMENTAL

The trialkyl(triaryl)-(p-bromophenoxy)silanes were obtained by the catalytic dehydrocondensation of trialkyl (triaryl)-silanes with p-bromophenol [2]. As catalysts we used zinc chloride in the synthesis of the triamyl- and trihexyl-(p-bromophenoxy)silanes, and stannous chloride in the synthesis of triphenyl- (p-bromophenoxy) silane. The amount of catalyst was 4.4 mole %, based on the taken silane. The reactants (silane and p-bromophenol) were taken in equimolar amounts. The properties and yields of the bromides are listed in Table 2.

### Synthesis of Methyl (p-Trialkylsiloxylphenyl) carbinols

**Experimental Procedure.** Into a 500-ml round-bottomed flask, fitted with a reflux condenser, dropping funnel and a stirrer, were charged 0.18 g-atom of magnesium and 70 ml of absolute ether. With constant stirring, a solution of the trialkyl-(p-bromophenoxy)-silane (0.09 g-mole) and ethyl bromide (0.09 g-mole) in 100 ml of absolute ether was added from the dropping funnel. Then the mixture was refluxed for 12 hr. After this the reaction mixture was cooled in a mixture of ice and water and then a solution of 0.54 g-mole of anhydrous acetaldehyde in 70 ml of absolute ether, cooled to 0°C, was added in drops. The mixture was refluxed for 30 hr, after which it was decomposed with pure water under cooling. A voluminous precipitate of basic magnesium salts was obtained, which proved to be difficult to remove by filtration. The ether layer from the filtration was dried over sodium sulfate, the ether was distilled off, and the reaction products were separated by fractional distillation.

**Synthesis of Methyl (p-Triamylsiloxylphenyl) carbinol.** The fractional distillation of the reaction products in vacuo gave the following fractions: 1st, 175–198°C (5 mm); 2nd, 198–207°C (5 mm); 3rd, 208–216°C (5 mm); residue (tar). The 1st fraction contained triamylphenoxysilane ( $n_D^{20}$  1.4817). Literature data for triamylphenoxysilane; b.p. 153°C (1.5 mm),  $n_D^{20}$  1.4800 [4]. The 2nd fraction had  $n_D^{20}$  1.4871 and was methyl (p-triamylsiloxylphenyl)-carbinol with a small amount of unreacted starting bromide. The 3rd fraction was pure methyl (p-triamylsiloxylphenyl)carbinol:

$n_D^{20}$  1.4885;  $d_4^{20}$  0.9589;  $MR_D$  114.9; Calc. 115.5

Found %: Si. 7.33, 7.21. M 369.9, 351.8.  $C_{23}H_{42}O_2Si$ . Calculated %: Si 7.41. M 378.6.

**Synthesis of methyl (p-trihexylsiloxylphenyl) carbinol.** The fractional distillation of the reaction products in vacuo gave the following fractions: 1st, 85–325°C (7 mm); 2nd, 233–238°C (6 mm); residue (tar). The 1st fraction was a mixture of methyl-(p-trihexylsiloxylphenyl)carbinol and trihexylphenoxysilane ( $n_D^{20}$  1.4768). The 2nd fraction was pure methyl (p-trihexylsiloxylphenyl)carbinol:

$n_D^{20}$  1.4990;  $d_4^{20}$  0.9654;  $MR_D$  127.3; calc. 129.5. Found %: Si 6.58, 6.51. M 420.6, 423.5.  $C_{26}H_{48}O_2Si$ . Calculated %: Si 6.68. M 420.7.

## SUMMARY

1. The catalytic dehydrocondensation of trialkyl (triaryl)silanes with p-bromophenol gave the previously unknown triamyl-, trihexyl- and triphenyl- (p-bromophenoxy)silanes.
2. The triamyl- and trihexyl- (p-bromophenoxy) silanes were converted via the Grignard synthesis to the previously unknown methyl-(p-triamylsiloxylphenyl)- and methyl-(p-trihexylsiloxylphenyl)- carbinols, whose properties and hydrolytic stability were studied.

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# CATALYTIC TRANSFORMATIONS OF TETRAALKYLSILANES

## IV. CATALYTIC DEHYDROGENATION OF TRIMETHYLETHYLSILANE

G. V. Golodnikov and G. N. Koroleva

Leningrad State University

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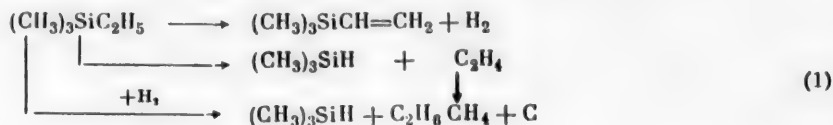
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In a previous paper [1] we discussed the results of studying the dehydrogenation of the trimethylpropyl-, trimethylbutyl- and trimethylhexylsilanes. It seemed of interest to us to also study the conditions for the dehydrogenation of trimethylethylsilane, the first member in the series of silicohydrocarbons of general formula  $(CH_3)_3SiR$ . Previously we had shown [1] that tetraethylsilane, in contrast to the mixed silanes, fails to undergo dehydrogenation under the conditions adopted by us, and instead only cleaves ethylene with the formation of the triethyl- and diethylsilanes. Apparently, this is explained by the symmetrical structure of tetraethylsilane and the high stability of the ethyl radicals.

The results of the experiments on the dehydrogenation of trimethylethylsilane (Table) testify to the fact that this reaction goes successfully only under quite drastic temperature conditions. The optimum temperature for the process (590-600°C) is higher than in the case of the silanes which contain propyl, butyl, or hexyl radicals (540-570°C). At 590°C and a space velocity of 45 the yield of trimethylvinylsilane was 11.3%, based on the silane passed through (one pass). Repeating the passage of the silane increased the yields of the silicoolefin considerably (more than 27% after the third pass).

Increasing the temperature to 620°C promotes the development of side reactions. Thermal decomposition and destructive hydrogenation of the starting silicohydrocarbon lead to the formation of trimethylsilane, ethylene and ethane. The presence of a coke deposit on the spent catalyst is evidence that decomposition of the ethylene takes place during the reaction.

The general scheme for the catalytic transformations of trimethylethylsilane is as follows:



The 54.8-55.0°C fraction, isolated from the fractional distillation of the condensates, is pure trimethylvinylsilane. Besides the constants, the purity of this fraction was also confirmed by determining the thiocyanogen number. According to the thiocyanogen number, the amount of silicoolefin in the fraction proved to be equal to 93.8%, whereas according to the data of A. A. Bugorkova and co-workers [2] the amount of double bond in pure trimethylvinylsilane, determined by thiocyanation for a day, is 95.5%. Bromination of the silicoolefin obtained by us gave 1-trimethylsilyl-1,2-dibromoethane in good yield.

All of the products of the side reactions were also isolated and identified. The conversion of trimethylsilane to trimethylsilanol was accomplished by the scheme:



The amounts of hydrogen, ethylene and saturated hydrocarbons were determined quantitatively using an All-Union Heat Engineering Institute gas analyzer. Bromination of the ethylene gave 1,2-dibromoethane.

## Dehydrogenation of Trimethylethylsilane

Temperature	Space velocity	Yld. condensate (% of silane passed through)	Thiocyanogen number of condensate	Amount of trimethylvinylsilane (in %)	Yield of trimethylvinylsilane (in % of silane passed through)	Amount in gas (in volume %)	
						H <sub>2</sub>	C <sub>2</sub> H <sub>4</sub>
500°	30	98.0	5.9	2.4	2.2	—	—
520	30	97.0	8.5	3.4	3.3	—	—
540	30	93.4	8.6	3.5	3.4	3.1	5.1
560	30	91.5	14.1	5.6	5.1	5.8	6.0
570	30	90.7	17.6	7.0	6.3	7.3	8.7
580	30	87.0	20.9	8.4	7.3	9.0	30.5
590	30	85.2	27.4	11.0	9.4	10.7	27.4
600	30	70.6	40.5	16.2	11.4	16.2	32.5
620	30	30.1	48.5	19.4	4.5	26.0	38.0
590	45	81.0	35.0	14.0	11.3	18.7	37.1
590	60	89.8	30.0	12.0	9.8	14.1	35.4
590	100	91.0	28.1	8.7	7.8	11.0	27.0
Repeated passage							
590	45	82.0	35.2	14.1	11.3 (1st passage)		
590	45	79.1	60.6	24.2	19.0 (2nd passage)		
590	45	77.3	88.0	35.2	27.1 (3rd passage)		

## EXPERIMENTAL

Trimethylethylsilane was prepared as described in [3] by the reaction of trimethylchlorosilane with Grignard reagent prepared from ethyl bromide. Yield 60%.

B. p. 61–62°C,  $d_4^{20}$  0.6850,  $n_D^{20}$  1.3830. According to [3]: b.p. 62°C,  $d_4^{20}$  0.6849,  $n_D^{20}$  1.3829.

Apparatus, general experimental procedure, catalyst, and method of analysis. All of these are described in [1].

Identification of Reaction Products. The condensates from all of the experiments were combined and distilled through a column with an efficiency of 30 theoretical plates. The following fractions were isolated: 1st, 12–14°C; 2nd, 42–53°C; 3rd, 54.8–55.0°C; 4th, 57–60°C; 5th, 61–62°C; and residue. The 1st fraction contained trimethylsilane (b.p. 9–11°C [4]). The 2nd fraction was an intermediate fraction ( $n_D^{20}$  1.3860). The 3rd fraction was pure trimethylvinylsilane.

B. p. 54.8–55.0°C;  $d_4^{20}$  0.6900;  $n_D^{20}$  1.3885,  $MR_D$  34.28. From the literature: b.p. 54.6°C (744 mm) [5],  $d_4^{20}$  0.6903 [5],  $n_D^{20}$  1.3880 [6], 1.3910 [5], 1.3852 [7],  $MR_D$  34.40 [6].

The 4th fraction was a mixture of trimethylvinylsilane and starting trimethylethylsilane. The amount of silicoolefin present, determined from the thiocyanogen number, was 81.0%. The 5th fraction was unchanged trimethylethylsilane ( $n_D^{20}$  1.3835,  $d_4^{20}$  0.6850). The residue from the distillation represented 2–3% and contained unchanged starting silane.

Conversion of Trimethylsilane to Trimethylsilanol. The 12–14°C fraction, obtained from the fractional distillation of the condensates, was cooled in a mixture of ice and water and then treated with a 0.5N solution of bromine in chloroform. After distilling off the chloroform, the trimethylbromosilane was distilled at a temperature of 80–81°C (b.p. 80°C [6]). An ether solution of the trimethylbromosilane was treated in the cold with 0.1N NaOH solution until neutral to phenolphthalein. The ether layer and extracts were dried over calcium chloride. After distilling off the ether, the fraction with b.p. 99–101°C was collected, representing trimethylsilanol:

$d_4^{20}$  0.8115,  $n_D^{20}$  1.3885, From [8] : b.p. 98.6–99.0°C;  $d_4^{20}$  0.8112;  $n_D^{20}$  1.3880.

Bromination of trimethylvinylsilane. With constant stirring and external cooling in dry ice, dry bromine was added slowly to the 54.8–55.0°C fraction. The reaction product was dried over calcium chloride and then fractionally distilled in vacuo to give pure 1-trimethylsilyl-1,2-dibromoethane.

B. p. 80°C (10 mm);  $d_4^{20}$  1.5492;  $n_D^{20}$  1.5090. From [9] : b.p. 74–75°C (8 mm);  $d_4^{20}$  1.5497;  $n_D^{20}$  1.5095.

Bromination of the gas from the experiments. Thirty milliliters of bromine was decolorized after the passage of 30 liters of the gas. The obtained substance was dried over calcium chloride and then subjected to fractional distillation. The following fractions were obtained: 1st, 80-81°C; 2nd, 130.5-132°C. The 1st fraction, being trimethylbromosilane, was added to the analogous fraction, obtained in the bromination of the 12-14°C fraction (see above). The 2nd fraction was 1,2-dibromoethane:

B. p. 130.5-132°C;  $d_4^{20}$  2.1782;  $n_D^{20}$  1.5375. From [10]: b.p. 131.7°C;  $d_4^{20}$  2.1785;  $n_D^{20}$  1.5379.

#### SUMMARY

The catalytic dehydrogenation of trimethylethylsilane was investigated.

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# TRIPHENOXYPHOSPHAZOARYLS

I. N. Zhmurova, I. Yu. Voitsekhovskaya  
and A. V. Kirsanov

Institute of Organic Chemistry of the Academy of Sciences of the Ukrainian SSR.

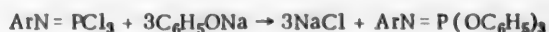
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When aromatic amines are acted on by phosphorus pentachloride they yield trichlorophosphazoaryls,  $\text{ArN}=\text{PCl}_3$ , or their dimers,  $(\text{ArN}=\text{PCl}_3)_2$ . The ability of the trichlorophosphazoaryls to dimerize depends on the degree of polarization of the N=P bond in their molecules: the stronger the polarization of the N=P bond, the more easily dimerization occurs. The polarization of the N=P bond, in turn, depends on the nature of the substituents in the aryl radical and on the phosphorus atom: electron-acceptor substituents in the aryl radical hinder polarization, and electron donors promote it [1]. The substituents on the phosphorus atom should act in the opposite direction. Consequently, replacement of the chlorine atoms by less electronegative atoms or groups of atoms should decrease the ability of the molecule to dimerize. Actually, while most of the trichlorophosphazoaryls are dimeric [1], triphenylphosphazoaryls,  $\text{ArN}=\text{P}(\text{C}_6\text{H}_5)_3$ , are monomeric [2]. It would be expected that triphenoxyphosphazoaryls,  $\text{ArN}=\text{P}(\text{OC}_6\text{H}_5)_3$ , also would be monomeric.

Until recently the triphenoxyphosphazoaryls have been difficult to obtain and therefore they have been studied comparatively little. The trialkoxyphosphazophenyls,  $\text{C}_6\text{H}_5\text{N}=\text{P}(\text{OAlk})_3$ , prepared by the reaction of phenyl azide with trialkyl phosphites [3], have been studied in more detail. Some triphenoxyphosphazoaryls have been prepared recently by the reaction of aromatic amines with pentaphenoxyphosphorus and triphenoxyphosphorus dichloride [4]. These methods of preparation are based on the utilization of comparatively unavailable starting materials and are therefore not very convenient. The molecular weights of the trialkoxy and triphenoxyphosphazoaryls have not been determined; on the basis of their physical properties, however, it must be supposed that they are monomeric. The triphenoxyphosphazoaryls can be prepared from the very readily available trichlorophosphazoaryls and sodium phenolate.



The triphenoxyphosphazoaryls are easily produced both from the monomeric and the dimeric trichlorophosphazoaryls. The formation of the triphenoxyphosphazoaryls from the dimeric trichlorophosphazoaryls is indirectly confirmed by the symmetrical structure of the latter [1]. As shown by molecular weight determinations, the triphenoxyphosphazoaryls exist only in the monomeric condition. The triphenoxyphosphazoaryls (Table 1), with the exception of the crystalline compounds (11), (16), and (21)-(23), are thick, very viscous liquids which do not distill without decomposition at 0.1-0.05 mm. Only unsubstituted triphenoxyphosphazophenyl distills in vacuum without decomposition. For the analysis and determination of the physical properties of compounds (2)-(10), (12)-(15), (17), (18), and (20) we employed the freshly prepared materials without additional purification. The analytical data and the satisfactory agreement of the calculated and observed molecular refractions indicate that the purity and identity of the compounds was satisfactory. The triphenoxyphosphazoaryls are hydrolyzed by water and moist air exceptionally rapidly, which greatly hampers work with them. We did not succeed in preparing compound (19) in the analytically pure state. Its structure and identity, however, were strictly enough demonstrated by conversion in 80% yield to the diphenyl ester of 2-nitrophenylamidophosphoric acid. All the triphenoxyphosphazoaryls are readily soluble in the usual organic solvents, with the exception of petroleum ether. When acted on by water they form the diphenyl esters of arylamidophosphoric acids (Table 2, method A).



Expt. No.	Ar	Yield (%)	External appearance	$d_4^{20}$	$n_D^{20}$	$M_n$		Formula	Found** (%)	Calcd. (%)
						Found	Calcd.			
10	3,5-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	70	Thick liquid	1.3155	1.6030	122.7	123.0	C <sub>24</sub> H <sub>18</sub> O <sub>3</sub> NCl <sub>2</sub> P	Cl 15.68, 15.95	Cl 15.10
11	2,4,6-Cl <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	78	Colorless needles, m.p. 68-69°	—	—	—	—	C <sub>24</sub> H <sub>17</sub> O <sub>3</sub> NCl <sub>3</sub> P	Cl 21.18, 21.45	Cl 21.11
12	<i>o</i> -BrC <sub>6</sub> H <sub>4</sub>	80	Thick liquid	1.3591	1.6069	121.9	121.1	C <sub>24</sub> H <sub>19</sub> O <sub>3</sub> NBrP	P 6.98, 6.55	P 6.45
13	<i>m</i> -BrC <sub>6</sub> H <sub>4</sub>	75	The same	1.3842	1.6060	124.1	121.1	C <sub>24</sub> H <sub>19</sub> O <sub>3</sub> NBrP	P 6.63, 6.07	P 6.45
14	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	83	"	1.3714	1.6099	121.3	121.1	C <sub>24</sub> H <sub>19</sub> O <sub>3</sub> NBrP {	P 6.45, 6.36. M 472, 496	P 6.45 M 480
15	2,4-Br <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	84	"	1.5222	1.6255	129.9	129.9	C <sub>24</sub> H <sub>18</sub> O <sub>3</sub> NBr <sub>2</sub> P	P 5.02, 5.35	P 5.54
16	2,4,6-Br <sub>3</sub> C <sub>6</sub> H <sub>2</sub>	70	Colorless needles, m.p. 68-69°	—	—	—	—	C <sub>24</sub> H <sub>17</sub> O <sub>3</sub> NBr <sub>3</sub> P	Br 38.23, 38.25	Br 37.61
17	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	88	Thick liquid	1.2093	1.5891	120.1	119.5	C <sub>28</sub> H <sub>22</sub> O <sub>4</sub> NP	P 7.19, 7.07	P 7.19
18	<i>p</i> -C <sub>2</sub> H <sub>5</sub> OC <sub>6</sub> H <sub>4</sub>	82	The same	1.2069	1.5862	123.8	124.2	C <sub>28</sub> H <sub>24</sub> O <sub>4</sub> NP {	P 6.36, 6.37. M 472, 485	P 6.96 M 445
19	<i>o</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	70	"	—	—	—	—	—	—	—
20	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	83	"	1.2665	1.6032	121.0	118.9	C <sub>24</sub> H <sub>19</sub> O <sub>3</sub> N <sub>2</sub> P	P 6.97, 6.66	P 6.95
21	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	70	Light yellow needles, m.p. 76-78° [4]	—	—	—	—	—	—	—
22	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	65	Light yellow needles, m.p. 78-80° [4]	—	—	—	—	—	—	—
23	2,6-Cl <sub>2</sub> -4-NO <sub>2</sub> C <sub>6</sub> H <sub>2</sub>	87	Light yellow needles, m.p. 90-92°	—	—	—	—	C <sub>24</sub> H <sub>17</sub> O <sub>3</sub> N <sub>2</sub> Cl <sub>2</sub> P	Cl 13.61, 13.61	Cl 13.68



Diphenyl Esters of Arylamidophosphoric Acids  $\text{ArNHPO}(\text{OC}_6\text{H}_5)_2$

Ex. No.	Ar	Yield (%) by method		Melting point	Formula	Found (%)	Calculated (%)
		A	B				
1	$\text{C}_6\text{H}_5$	80	95	129–130° [4]	—	—	—
2	<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4$	68	94	121–123°	$\text{C}_{19}\text{H}_{18}\text{O}_3\text{NP}$	N 4.33, 4.26	N 4.13
3	<i>m</i> - $\text{CH}_3\text{C}_6\text{H}_4$	95	94	122–123	$\text{C}_{19}\text{H}_{18}\text{O}_3\text{NP}$	N 4.43, 4.28	N 4.13
4	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4$	95	70	138–140 [5]	—	—	—
5	$3,5\text{-(CH}_3)_2\text{C}_6\text{H}_3$	59	71	132–133	$\text{C}_{20}\text{H}_{20}\text{O}_3\text{NP}$	N 3.92, 3.96	N 3.96
6	<i>o</i> - $\text{ClC}_6\text{H}_4$	94	80	120–122	$\text{C}_{18}\text{H}_{15}\text{O}_3\text{NClP}$	Cl 9.67, 9.98	Cl 9.87
7	<i>m</i> - $\text{ClC}_6\text{H}_4$	98	92	100–102	$\text{C}_{18}\text{H}_{15}\text{O}_3\text{NClP}$	Cl 9.89, 9.87	Cl 9.87
8	<i>p</i> - $\text{ClC}_6\text{H}_4$	80	63	117–118 [6]	—	—	—
9	$2,4\text{-Cl}_2\text{C}_6\text{H}_3$	95	84	71–73°	$\text{C}_{18}\text{H}_{14}\text{O}_3\text{NCl}_2\text{P}$	Cl 17.98, 18.14	Cl 18.00
10	$3,5\text{-Cl}_2\text{C}_6\text{H}_3$	95	79	115–116	$\text{C}_{18}\text{H}_{14}\text{O}_3\text{NCl}_2\text{P}$	Cl 18.39, 18.44	Cl 18.00
11	$2,4,6\text{-Cl}_3\text{C}_6\text{H}_2$	97	—	142–143	$\text{C}_{18}\text{H}_{13}\text{O}_3\text{NCl}_3\text{P}$	Cl 25.11, 25.26	Cl 24.83
12	<i>o</i> - $\text{BrC}_6\text{H}_4$	98	83	122–123	$\text{C}_{18}\text{H}_{15}\text{O}_3\text{NBrP}$	Br 19.48, 19.60	Br 19.80
13	<i>m</i> - $\text{BrC}_6\text{H}_4$	98	83	117–119	$\text{C}_{18}\text{H}_{15}\text{O}_3\text{NBrP}$	Br 19.81, 19.99	Br 19.80
14	<i>p</i> - $\text{BrC}_6\text{H}_4$	98	75	110–112 [7]	—	—	—
15	$2,4\text{-Br}_2\text{C}_6\text{H}_3$	93	85	86–88°	$\text{C}_{18}\text{H}_{14}\text{O}_3\text{NBr}_2\text{P}$	Br 32.90, 32.89	Br 33.12
16	$2,4,6\text{-Br}_3\text{C}_6\text{H}_2$	90	—	165–166	$\text{C}_{18}\text{H}_{13}\text{O}_3\text{NBr}_3\text{P}$	Br 43.12, 43.40	Br 42.70
17	<i>p</i> - $\text{CH}_3\text{OC}_6\text{H}_4$	50	88	139–141	$\text{C}_{19}\text{H}_{18}\text{O}_4\text{NP}$	N 4.05, 4.21	N 3.94
18	<i>p</i> - $\text{C}_2\text{H}_5\text{OC}_6\text{H}_4$	50	90	109–110	$\text{C}_{20}\text{H}_{20}\text{O}_4\text{NP}$	N 4.06, 3.89	N 3.79
19	<i>o</i> - $\text{NO}_2\text{C}_6\text{H}_4$	82	60	108–109	$\text{C}_{18}\text{H}_{15}\text{O}_5\text{N}_2\text{P}$	N 7.27, 7.46	N 7.57
20	<i>m</i> - $\text{NO}_2\text{C}_6\text{H}_4$	87	75	127–128	$\text{C}_{18}\text{H}_{15}\text{O}_5\text{N}_2\text{P}$	N 7.78, 7.98	N 7.57
21	<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	98	75	146–148 [4]	—	—	—
22	$2,4\text{-(NO}_2)_2\text{C}_6\text{H}_3$	92	—	144–146 [4]	—	—	—
23	$2,6\text{-Cl}_2\text{-4-NO}_2\text{C}_6\text{H}_2$	84	—	159–161	$\text{C}_{18}\text{H}_{13}\text{O}_5\text{N}_2\text{Cl}_2\text{P}$	Cl 16.15, 16.35	Cl 16.17

Triphenoxyphosphazonyls  $\text{ArN}=\text{P}(\text{OC}_6\text{H}_5)_3$

Expt. No.	Ar	Yield (%)	External appearance	$d_4^{20}$	$n_D^{20}$	$M R_D^*$		Formula	Found <sup>a</sup> (%)	Calculated (%)
						Found	Calcd.			
1	$\text{C}_6\text{H}_5$	75	Thick liquid, b.p. 222-224° (0.05 mm) [4]	1.2085	1.6005	113.6	113.3	$\text{C}_{24}\text{H}_{20}\text{O}_3\text{NP}$	P 8.07, 8.07	P 7.73
2	<i>o</i> - $\text{CH}_3\text{C}_6\text{H}_4$	82	Thick liquid	1.2080	1.6006	117.5	118.0	$\text{C}_{25}\text{H}_{22}\text{O}_3\text{NP}$	P 7.19, 7.26	P 7.47
3	<i>m</i> - $\text{CH}_3\text{C}_6\text{H}_4$	76	The same	1.2023	1.5942	117.2	118.0	$\text{C}_{25}\text{H}_{22}\text{O}_3\text{NP}$	P 7.18, 7.55	P 7.47
4	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4$	83	» »	1.2032	1.5969	117.5	118.0	$\text{C}_{25}\text{H}_{22}\text{O}_3\text{NP}$	P 7.25, 7.78	P 7.47
5	3,5-( $\text{CH}_3$ ) $_2\text{C}_6\text{H}_3$	85	» »	1.1809	1.5935	123.2	122.5	$\text{C}_{26}\text{H}_{24}\text{O}_3\text{NP}$	P 7.01, 6.95, M 400, 419	P 7.22 M 429
6	<i>o</i> - $\text{ClC}_6\text{H}_4$	85	» »	1.2605	1.6048	119.0	118.2	$\text{C}_{24}\text{H}_{19}\text{O}_3\text{NCIP}$	P 6.61, 6.88	P 7.12
7	<i>m</i> - $\text{ClC}_6\text{H}_4$	75	» »	1.2606	1.6035	118.7	118.2	$\text{C}_{24}\text{H}_{19}\text{O}_3\text{NCIP}$	P 6.67, 6.61, M 402, 399	P 7.12 M 436
8	<i>p</i> - $\text{ClC}_6\text{H}_4$	80	» »	1.2599	1.5980	117.9	118.2	$\text{C}_{24}\text{H}_{19}\text{O}_3\text{NCIP}$	P 7.00, 7.45, M 449, 463	P 7.12 M 436
9	2,4- $\text{Cl}_2\text{C}_6\text{H}_3$	76	» »	1.3113	1.6082	124.0	123.0	$\text{C}_{24}\text{H}_{18}\text{O}_3\text{NCl}_2\text{P}$	P 5.89, 6.06, M 479, 438	P 6.59 M 470

The latter were synthesized also by the action of aromatic amines on diphenyl chlorophosphate (Table 2, Method B).



With weakly basic amines the reaction was carried out in pyridine solution.

#### EXPERIMENTAL

Triphenoxyphosphazoyls (Table 1). All the work had to be carried out under conditions which excluded as far as possible the reaction of the mixtures and the compounds with the moisture of the air. All the solvents had to be carefully dried. A mixture of 0.02 mole of the monomeric or dimeric trichlorophosphazoyl, 50 ml of benzene, and 0.06 mole of sodium phenolate was refluxed for 3 hours and left over night. The sodium chloride was filtered off with suction and the filtrate was evaporated in vacuum on a water bath. The triphenoxyphosphazoyls remained in the form of thick, viscous oils. Triphenoxyphosphazophenyl was distilled in vacuum. Compounds (2)-(10), (12)-(15), and (17)-(20) were not further purified. Compounds (11), (16), and (21)-(23) crystallized when rubbed with a glass stirring rod. The crystals were treated with cold anhydrous alcohol filtered with suction, dried in vacuum, and recrystallized from anhydrous alcohol.

Diphenyl ester of Arylamidophosphoric Acids (Table 2). From triphenoxyphosphazoyls (method A). To 0.01 mole of triphenoxyphosphazoyl were added 10-15 ml of water and 1-2 drops of concentrated hydrochloric acid. The mixture was left to stand for a day. The crystalline ester was filtered with suction, washed with water, with 1-2% sodium hydroxide solution, and again with water, dried in the air, and recrystallized from alcohol. Crude (2), (5), (17), and (18) were treated with cold alcohol to remove oily impurities.

From Diphenyl Chlorophosphate and Amines (Method B). A mixture of 0.1 mole of diphenyl chlorophosphate, 10 ml of benzene, and 0.2 mole of amine was refluxed for 1 hour. The benzene was distilled off in vacuum on a water bath, the residue was treated with water, and the crystalline diester was filtered off with suction, dried in the air, and recrystallized from a alcohol. In this manner compound (1) - (8), (12)-(14), (17), and (18) were prepared. Compounds (9), (10), (15), and (19)-(21) were prepared in the following way: to a solution of 0.01 mole of diphenyl chlorophosphate in 10 ml of pyridine was added 0.01 mole of amine. The reaction was accompanied by slight evolution of heat. After several hours the mixture was diluted with water and the precipitate of diester that separated out was filtered off with suction, washed with water, dried, and recrystallized from alcohol. The identity of the diesters obtained by methods A and B was demonstrated by mixed melting points. Compounds (11), (16), (22), and (23) could not be obtained from diphenyl chlorophosphate and the corresponding amines even by boiling in pyridine for several hours.

#### SUMMARY

1. The dimeric and monomeric trichlorophosphazoyls on reaction with sodium phenolate form monomeric triphenoxyphosphazoyls.

2. When the triphenoxyphosphazoyls are hydrolyzed, diphenyl esters of the arylamidophosphoric acids are formed, which also are obtained by the action of the aromatic amines on diphenyl chlorophosphate.

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# TRIANILIDOPHOSPHAZOAROYLS AND N-DIANILIDOPHOSPHINYL-N'-ARYLARENAMIDINES.

G. I. Derkach, E. S. Gubnitskaya, and A. V. Kirsanov

Institute of Organic Chemistry of the Academy of Sciences of the Ukrainian SSR.

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When aromatic amines act on trichlorophosphazosulfonyls, the replacement of two atoms of chlorine by anilido groups takes place readily and dianilidomonochlorophosphazosulfonyls are formed. Only on prolonged heating with an excess of the aromatic amine does replacement of the third chlorine atom take place and the trianilidophosphazosulfonyls form [1]. The chlorine atoms in trichlorophosphazoaryls are replaced by anilido groups considerably more easily. Even on short boiling in benzene solution almost quantitative yields are produced of the trianilidophosphazoaryls (Table 1), which are colorless, crystalline, neutral compounds that melt with decomposition.

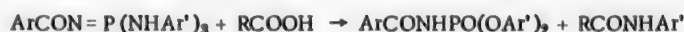


With respect to their chemical properties the trianilidophosphazoaryls differ distinctly from trianilidophosphazosulfonyls [1] and -alkyls [2]. The latter are very difficult to hydrolyze with aqueous solutions of acids and alkalis and are not hydrolyzed at all by boiling in water. The trianilidophosphazoaryls are hydrolyzed very easily and in this respect are similar to the triaroxyposphazoaryls [3]. Hydrolysis occurs practically quantitatively upon boiling for a few minutes with 96% ethanol and the dianilides of the aroylamidophosphoric acids are formed.



Hydrolysis occurs readily even by the moisture of the air, and it is therefore necessary to prepare and isolate the trianilidophosphazoaryls under conditions which exclude reaction with the moisture of the air.

The trianilidophosphazoaryls, like the full amides of sulfuric acid [4] and some amides of phosphoric [5] and phosphonic acids [6], are active arylamidating agents. They arylamidate carboxylic acids not only in the presence of pyridine, but also in dioxane solution.



Arylamidating properties are shown not only by the triphenylamidophosphazoaryls, but also by the tris (p-tolylamido)phosphazoaryls, in contrast to the trianilides of phosphoric acid, among which the triphenylamidophosphates phenylamidate carboxylic acids, but the tris (p-tolylamido)phosphates do not [5].

The N-dianilidophosphinyl-N'-arylarenamidines (Table 2), which are isomeric with the trianilidophosphazoaryls, are obtained easily and in good yields by the action of aromatic amines on N-dichlorophosphinylimidocarbonylic acid chlorides.



The N-dianilidophosphinyl-N'-arylarenamidines are colorless, crystalline neutral compounds, insoluble in aqueous solutions of acids and alkalis and melting with decomposition. In contrast to the trianilidophosphazoaryls they are very stable to hydrolysis and are practically unchanged by boiling for many hours in aqueous alcoholic solutions of acids and alkalis.

## EXPERIMENTAL

Trianilidophosphazoaryls (Table 1). All of the solvents used had to be dry. All operations had to be carried out under conditions that excluded as far as possible access of moisture of the air to the reaction mixture and the end products. To a solution of 0.01 mole of trichlorophosphazoaryl in 30-40 ml of benzene, was added slowly,

of the type  $\text{ArCON}=\text{P}(\text{NHR}')_3$

Found (%)	Formula	Calculated (%)	Solubility*				
			Benzene	Dioxane	Ether	$\text{CH}_2\text{Cl}_2$	$\text{CCl}_4$
N 13.50, 13.52	$\text{C}_{25}\text{H}_{23}\text{ON}_4\text{P}$	N 13.14	+	—	=	+	—
P 6.82, 6.01	$\text{C}_{28}\text{H}_{20}\text{ON}_4\text{P}$	P 6.61	+	+	=	+	+
P 5.69, 5.78	$\text{C}_{25}\text{H}_{22}\text{ON}_4\text{PBr}$	P 6.13	+	+	=	—	—
P 5.75, 5.84	$\text{C}_{28}\text{H}_{28}\text{ON}_4\text{PBr}$	P 5.66	+	+	—	—	+
P 5.80, 5.89	$\text{C}_{25}\text{H}_{22}\text{O}_3\text{N}_5\text{P}$	P 6.57	—	—	=	—	—
N 13.53, 13.59	$\text{C}_{28}\text{H}_{28}\text{O}_3\text{N}_5\text{P}$	N 13.63	—	—	=	—	—
N 14.30, 14.45	$\text{C}_{25}\text{H}_{22}\text{O}_3\text{N}_5\text{P}$	N 14.86	—	+	=	+	—
N 13.17, 13.34	$\text{C}_{28}\text{H}_{20}\text{O}_3\text{N}_5\text{P}$	N 13.63	+	+	=	+	+

point, = insoluble at boiling point. All compounds were insoluble in petroleum ether and

solution.

solution.

arenamidines of the Type  $\text{ArC}[\text{=NPO}(\text{NHR}')_2]\text{NHR}'$

Found (%)	Formula	Calculated (%)	Solubility**				
			Ethanol	Methanol	Benzene	Acetone	Ether
P 7.17, 7.31	$\text{C}_{25}\text{H}_{23}\text{ON}_4\text{P}$	P 7.21	+	+	+	+	+
P 6.85, 7.03	$\text{C}_{28}\text{H}_{20}\text{ON}_4\text{P}$	P 6.61	+	+	+	+	—
P 5.66, 5.69;	$\text{C}_{25}\text{H}_{22}\text{ON}_4\text{PBr}$	P 6.13;	+	—	+	+	=
N 10.59, 10.64		N 11.09					
N 9.62, 9.76;	$\text{C}_{28}\text{H}_{28}\text{ON}_4\text{PBr}$	N 10.23;	+	+	+	+	=
Br 14.33, 14.41		Br 14.59					
P 6.15, 6.24	$\text{C}_{25}\text{H}_{22}\text{O}_3\text{N}_5\text{P}$	P 6.57	+	+	+	+	=
N 13.57, 13.53	$\text{C}_{28}\text{H}_{28}\text{O}_3\text{N}_5\text{P}$	N 13.63	+	+	+	+	=
N 14.80, 14.84	$\text{C}_{25}\text{H}_{22}\text{O}_3\text{N}_5\text{P}$	N 14.86	+	+	—	+	=
P 6.03, 6.18	$\text{C}_{28}\text{H}_{28}\text{O}_3\text{N}_5\text{P}$	P 6.03	+	+	+	+	=

carbon tetrachloride and petroleum ether, insoluble in water.

solution.

solution.

Trianilidophosphoroyls

Ar	Ar'	Yield (%)	External appearance of crystals	Melting point
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	90	Fine platelets***	112—115°
C <sub>6</sub> H <sub>5</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	80	Fine platelets****	101—103
p-BrC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	98	Platelets****	99—101
p-BrC <sub>6</sub> H <sub>4</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	77	Platelets****	84—86
m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	98	Platelets****	81—83
m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	91	Platelets, methylene chloride	140—142
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	78	Prisms, benzene	207—209
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	94	Prisms, benzene	213—214

\* All compounds melted with decomposition.

\*\*‡ Readily soluble at 20°, + readily soluble at boil-point, - difficultly soluble at boiling decomposed under the influence of water.

\*\*\* The compound was purified by reprecipitation with ether from methylene chloride

\*\*\*\* The compound was purified by reprecipitation with petroleum ether from benzene

N-Dianilidophosphinyl-N'-aryl-

Ar	Ar'	Yield (%)	External appearance of crystals	Melting point *
C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	99	Fine platelets***	93—95°
C <sub>6</sub> H <sub>5</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	95	Fine platelets****	94—96
p-BrC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	99	Prisms, benzene	190—191
p-BrC <sub>6</sub> H <sub>4</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	99	Platelets, alcohol	145—146
m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	99	Concretions of needles, acetone, alcohol	102—103
m-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	99	Fine prisms, acetone, alcohol	116—117
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	85	Prisms, alcohol	198—199
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	99	Prisms, alcohol	220—221

\* All compounds melted with decomposition.

\*\* Designations as in Table 1. All compounds were very difficultly soluble in boiling

\*\*\* The compound was purified by reprecipitation with petroleum ether from benzene

\*\*\*\* The compound was purified by reprecipitation with petroleum ether from ether



with vigorous stirring, a solution of 0.06 mole of aromatic amine in 20-30 ml of benzene. The reaction proceeded with slight evolution of heat ( $\sim 50^{\circ}\text{C}$ ). The mixture was boiled for 1 hour, cooled to  $20^{\circ}\text{C}$ , the amine hydrochloride that had precipitated was filtered off with suction, and the filtrate was evaporated in vacuum. In the residue there was a viscous oil which gradually crystallized upon trituration with petroleum ether. The crystalline product was filtered off with suction and recrystallized or reprecipitated.

N-Dianilidophosphinyl-N'-arylbenzamides (Table 2). To a solution of 0.01 mole of N-dichlorophosphinylimidocarboxylic acid chloride in 10-15 ml of dry dioxane was added, with vigorous stirring, a solution of 0.06 mole of aromatic amine in 5 ml of dioxane. The reaction proceeded with slight evolution of heat ( $\sim 50^{\circ}\text{C}$ ). The mixture was left at  $20^{\circ}\text{C}$  for 10-15 hours, the amine hydrochloride that had settled out was filtered off with suction, and the filtrate was evaporated in vacuum. In the residue there was a dense crystalline mass or a thick oil which gradually crystallized upon treatment with aqueous methanol. The crystals were filtered off with suction, washed with water (twice with 20 ml), and recrystallized. It also was possible to distill off the solvent from the reaction mixture without filtering out the amine hydrochloride, treat the residue with water and then with a small amount (3-5 ml) of methanol.

Hydrolysis of Trianilidophosphazaroyle. A mixture of 0.001 mole of trianilidophosphazaroyle and 15 ml of 96% alcohol was heated to boiling. The trianilido compound went into solution. Upon cooling, the dianilide of the aroylamidophosphoric acid precipitated and was filtered out with suction, washed, and dried. The yields were about 90% and identification was by mixed melting points.

Arylamidation of Carboxylic Acids by the Action of Trianilidophosphazaroyle. A mixture of 0.02 mole of carboxylic acid, 0.02 mole of trianilidophosphazaroyle, and 5 ml of pyridine was heated for 4 hours on an oil bath at  $120-130^{\circ}\text{C}$ . The pyridine was distilled off in vacuum and the residue was carefully mixed with 10 ml of 2 N aqueous sodium carbonate solution, the crystalline precipitate was filtered with suction, washed with water, carefully dried, ground, and extracted several times with ether. The ether solution was evaporated; in the residue were the anilides of the carboxylic acids, which were purified by the usual methods. The compounds prepared were the benzanilide (73% yield), the p-nitrobenzanilide (68% yield), the acetanilide (65% yield), the benzo-p-toluidide (82% yield), and the aceto-p-toluidide (60% yield). Identification was by mixed melting points. When the reaction was carried out in dioxane solution, the acetanilide was obtained in 55% yield.

Boiling N-di-p-toluididophosphinyl-N'-p-tolylbenzamide with alkali. A mixture of 0.01 mole of the amidine, 40 ml of ethanol, and 6 ml of 2 N aqueous sodium hydroxide solution was refluxed for 16 hours, the solution was neutralized with hydrochloric acid and evaporated to dryness in vacuum; from the residue unchanged N-di-p-toluididophosphinyl-N'-tolylbenzamide was isolated in 90% yield. Identification was by mixed melting point.

#### SUMMARY

When aromatic amines act on trichlorophosphazaroyle, trianilidophosphazaroyle are produced, which are very easily hydrolyzed to dianilides of aroylamidophosphoric acids and are arylamidating agents for carboxylic acids in pyridine and dioxane solutions. When aromatic amines act on N-dichlorophosphinylimidocarboxylic acid chlorides, neutral, very difficultly hydrolyzed N-dianilidophosphinyl-N'-arylamides are produced.

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## LXXXVI. ALKYL MERCAPTO (DIETHYLAMINO) BORANES\*

B. M. Mikailov and V. A. Dorskhov

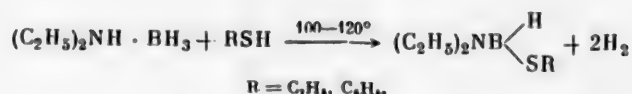
Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 11,

pp. 3750-3756, November, 1961

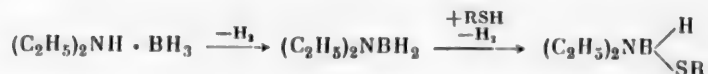
Original article submitted December 6, 1960

Recently we reported the preparation of a new and interesting class of compounds, the alkylmercapto (dialkylamino) boranes [1]. By heating n-propyl- or n-butylmercaptan with diethyl amine-borane at 100-120°C we synthesized the corresponding n-propylmercapto (diethylamino) borane and n-butylmercapto (diethylamino) borane. By means of this reaction it is possible, starting with complexes of borane with aliphatic, aromatic, or cyclic amines, to obtain very diverse representatives of this class of compounds in high yields (80-90%).

In the present article we describe the preparation by this method of another two such compounds, ethylmercapto (diethylamino) borane and phenylmercapto (diethylamino) borane.

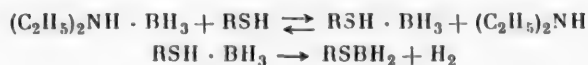


It might be assumed that the mechanism of this reaction consists in the thermal conversion of the diethyl amine-borane to diethylaminoborane, which further reacts with the mercaptan to form the final product. In favor of this assumption is the ability of diethylaminoborane to give alkylmercapto(diethylamino)boranes on reaction with mercaptans [1].



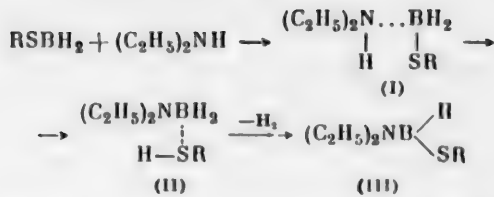
The dehydrogenation of diethyl amine-borane to diethylaminoborane, however, requires considerably longer heating at a higher temperature (130-150°C) than is necessary for carrying out the reaction of diethyl amine-borane with mercaptans, and the latter therefore obviously follows a different route.

Apparently the mercaptan to some extent displaces the diethyl amine from the starting complex and the resulting complex of borane with the mercaptan is thermally converted with the splitting out of hydrogen to the alkylmercaptoborane.



The alkylmercaptoborane which is produced combines with the diethyl amine in a complex (I), which then breaks down into diethylaminoborane and mercaptan, in a manner similar to the behavior of ethylmercaptoborane with respect to primary amines [2]. The diethylaminoborane further gives a complex (II) with the mercaptan. The conversions mentioned are equivalent to the direct formation of complexes (I) and (II). In the last stage, complex (II) splits out hydrogen and is converted to the alkylmercapto(diethylamino) borane (III).

\* For LXXXV see DAN 139, 385 (1961).



The alkylmercapto(diethylamino)boranes are colorless mobile liquids with an unpleasant odor. They have considerable thermal stability and are not decomposed nor symmetrized at about 200°C.

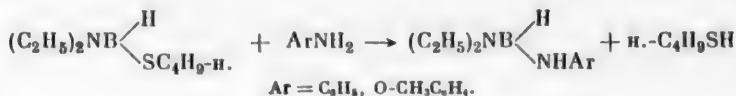
Determination of the molecular weights by the cryoscopic method and the comparatively low boiling points of the alkylmercapto-(diethylamino)boranes indicate that they exist in the monomeric form.

This characteristic of the alkylmercapto(dialkylamino)boranes can be compared with the tendency of other substituted boranes to dimerize. As is well known, the dialkylaminoboranes [3,1] exist in the dimeric form, but derivatives of borane with two dialkylamino groups are monomeric [4].

Hence we may conclude that for the disubstituted boranes dimerization is energetically disadvantageous if there are on the boron atom two atoms with incomplete electron pairs, for example two nitrogen atoms, as in bis (dialkylamino) boranes, or atoms of nitrogen and sulfur, as in alkylmercapto(diethylamino) boranes. Compounds of borane with two atoms of sulfur on the boron, however, such as the dialkylmercaptoboranes, exist in the dimeric form [2]. Further investigation is necessary to find an explanation of the interesting facts about the effect of the nature and the number of the substituents in borane derivatives on their tendency to dimerize.

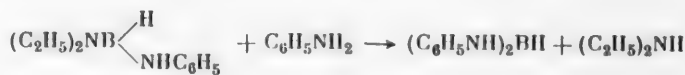
The study of the chemical properties of the alkylmercapto(diethylamino) boranes is a very interesting problem, since it allows an explanation of the relative lability of the hydrogen atom and the diethylamino and alkylmercapto groups attached to one boron atom.

We first investigated the behavior of the alkylmercapto(diethylamino)-boranes with relation to primary and secondary amines. It was found that aromatic primary amines—*aniline* and *o*-toluidine—react with *n*-butylmercapto (diethylamino) borane under very mild conditions. In this process the *n*-butylmercapto group is replaced by the arylamino group and mixed substituted diaminoboranes—phenylamino(diethylamino) borane and *o*-tolylamino (diethylamino) borane—are obtained in 60-70 % yield.



It should be noted that when aniline is added to n-butylmercapto(diethylamino) borane at 10°C a crystalline precipitate separates, which probably is a complex and disappears upon gradual warming of the reaction mixture to room temperature.

The arylamino(diethylamino)borane in turn is capable of reacting with aniline at 60-80°C. In this process not hydrogen, but the diethylamino group is replaced by the phenylamino group.

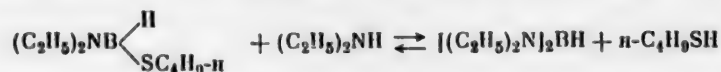


The bis(phenylamino)borane produced forms colorless needles, which dissolve well in benzene and ether, and poorly in hexane. It reacts violently with alcohol at room temperature with the evolution of hydrogen. Bis(phenylamino) borane also exists in monomeric form,

Mikheeva and Fedneva [5] obtained by the action of diborane on aniline a substance for which they established, on the basis of analysis for boron, nitrogen, and active hydrogen, the composition  $(C_6H_5)_2N_2BH$ . They suggested

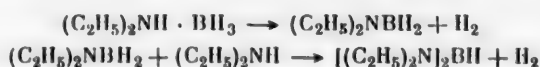
that the compound had the structure  $(C_2H_5NH)_2BH$ . The authors did not indicate the melting point and yield of the compound.

Under other conditions alkylmercapto(diethylamino)boranes react with secondary aliphatic amines. In the cold *n*-butylmercapto(diethylamino)borane does not react with diethyl amine. If the mixture is boiled for 5 hours, however, then half of the *n*-butylmercapto(diethylamino) borane taken for the experiment is converted to bis(diethylamino) borane, but the second half remains unchanged. Further heating of the reaction mixture does not increase the yield of the bis(diethylamino) borane, which indicates the existence of an equilibrium:



The same equilibrium mixture can be arrived at by heating bis(diethylamino) borane with *n*-butylmercaptan. This reaction is the first case of replacement of an alkylamino group on a boron atom by an alkylmercapto group. Usually the reverse process takes place—replacement of alkylmercapto groups on a boron atom by alkylamino groups. Similar exchange reactions are observed when amines act on esters of thioboro organic acids [6,7]. When there are two alkylmercapto groups on a boron atom, however, as in esters of alkylthioboric acids, for example, then under the action of diethyl amine only one alkylmercapto group is replaced by the diethylamino group and the second does not react, so that as a result an alkyl(diethylamino) (alkylmercapto) boron is obtained [9].

We also prepared bis(diethylamino) borane in another way, namely by slow addition of diethyl amine to diethylamine-borane heated to 130–150°C.

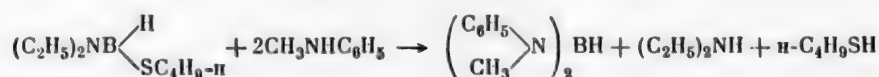


The first representative of the bis(dialkylamino) boranes, namely bis(dimethylamino) borane, had been prepared previously [4] by heating dimethylaminoborane with dimethyl amine at 150–200°C.

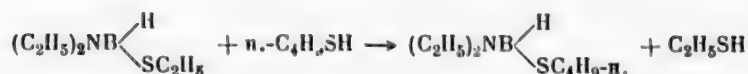
If methylaniline acts on *n*-butylmercapto(diethylamino) borane, simultaneous replacement of both the diethylamino and the *n*-butylmercapto groups occurs.

Thus when an equimolar mixture of the reagents mentioned is heated slightly, bis(*N*-methyl-*N*-phenylamino) borane is obtained in 42% yield and about half of the starting *n*-butylmercapto (diethylamino) borane does not react.

If, however, the starting reagents are used in the ratio 1 : 2, then bis (*N*-methyl-*N*-phenylamino) borane is obtained in 83% yield. Like the other substituted diaminoboranes, this compound is monomeric.



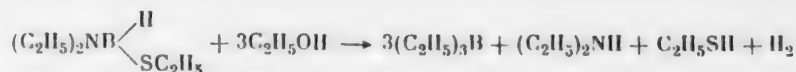
The conversions of *n*-butylmercapto(diethylamino)borane by the action of amines indicate the great lability of the  $R_2N$ - and  $RS$ -groups in comparison with the hydrogen. The comparative inertness of the hydrogen atom in these compounds also is illustrated by the fact that we did not succeed in replacing it by an alkylmercapto group even by heating the alkylmercapto(dialkylamino) borane with the mercaptan at 200°C. If an alkylmercapto(diethylamino) borane is heated with a higher mercaptan, the lower mercapto group is replaced by the higher one. Thus, when ethylmercapto(diethylamino) borane is boiled with *n*-butylmercaptan, *n*-butylmercapto(diethylamino) borane and ethylmercaptan are produced smoothly.



Ethyl alcohol at room temperature reacts violently with alkylmercapto(diethylamino) boranes with the evolution of hydrogen. In this case, however, the  $RS$ - and  $R_2N$  groups first react, and then the dialkoxyborane that has been produced either reacts directly with the alcohol with the evolution of hydrogen, or it is symmetrized to the

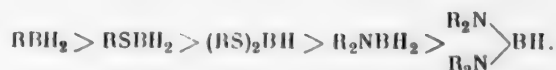
orthoborate and diborane and the latter reacts with the alcohol.

This is evident from the fact that if we add dropwise an equimolar quantity of alcohol to an ether solution of ethylmercapto(diethylamino) borane at  $-10^{\circ}\text{C}$ , hydrogen is evolved in completely insignificant amount. If a second equivalent of alcohol is added, 50-60% of the theoretical amount of hydrogen is evolved; this evolution continues if new portions of alcohol are added and ceases after the addition of a total of three equivalents of alcohol.



The slight lability of the hydrogen atom in the alkylmercapto(diethylamino)boranes also is evident in their inability to add to unsaturated hydrocarbons even at  $120^{\circ}\text{C}$  in the presence of pyridine, i.e., under the same conditions where bis(diethylamino) diborane forms bis (diethylamino)-(n-butyl)borane with butylene. The addition of borane and its derivatives to unsaturated compounds takes place with the participation of hydride ions. These reactions take place the more readily the greater the density of the electron cloud at the B-H bond, i.e., the more easily heterolytic rupture of this bond occurs. As a result of the inductive effect of the electronegative nitrogen and sulfur atoms in the alkylmercapto(diethylamino) boranes the density of the electron cloud at the B-H bond is so much diminished that these compounds do not add at a double bond.

The various derivatives of borane can be arranged in the following order according to their tendency to enter into addition reactions with unsaturated compounds:



Actually, the diaryldiboranes react with unsaturated hydrocarbons at  $-40^{\circ}\text{C}$  [9], the dialkylmercaptodiboranes add to olefins at room temperature [10], and the tetraalkylmercaptodiboranes add to olefins on heating in the presence of pyridine [11].

Bis(diethylamino) diborane, as already indicated, adds to butylene with still greater difficulty [1], requiring heating at  $120^{\circ}\text{C}$ .

All the monomeric derivatives of borane obtained are easily hydrolyzed and are oxidized in the air.

#### EXPERIMENTAL

All of the operations were carried out in an atmosphere of dry nitrogen.

Ethylmercapto(diethylamino) borane. In a three-necked flask fitted with a thermometer, dropping funnel, and a condenser cooled with a mixture of dry ice and actone was placed 9.7 g of diethylamine-borane and 8.1 g of ethylmercaptan was added dropwise at  $100-110^{\circ}\text{C}$  over the course of 4 hours. Upon distillation 14.5 g (89%) of ethylmercapto(diethylamino) borane was obtained.

B. p.  $65-67^{\circ}\text{C}$  at 19 mm,  $d_4^{20}$  0.8502,  $n_D^{20}$  1.4616.

Found %: C 50.12; H 11.13.  $\text{C}_6\text{H}_{16}\text{NSB}$ . Calculated %: C 49.66; H 11.11.

Phenylmercapto(diethylamino) borane. A mixture of 9.0 g of diethyl amine-borane and 11.5 g of thiophenol was heated at  $110-120^{\circ}\text{C}$  for 1 hour. Upon fractional distillation 15.2 g (79%) of phenylmercapto(diethylamino) borane was obtained.

B. p.  $82-84^{\circ}\text{C}$  at 1.5 mm,  $d_4^{20}$  0.9736,  $n_D^{20}$  1.5470.

Found %: C 62.46; H 8.71.  $\text{C}_{10}\text{H}_{16}\text{NSB}$ . Calculated %: C 62.19; H 8.35.

Phenylamino(diethylamino) borane. To 18.5 g of n-butylmercapto(diethylamino) borane cooled to  $-15-10^{\circ}\text{C}$  was added dropwise, with stirring, 10.5 g of aniline. A crystalline precipitate separated out, which then disappeared when the temperature was raised to that of the room. Stirring was continued for another 0.5 hour. Upon fractional distillation 13.2 g (70%) of phenylamino(diethylamino) borane was obtained.



B.p. 80-82°C at 1.5 mm,  $d_4^{20}$  0.9234,  $n_D^{20}$  1.5295.

Found %: C 67.99; H 9.90; B 6.47. M 172.3.  $C_{10}H_{17}N_2B$ . Calculated %: C 68.21; H 9.73; B 6.15; M 176.1.

In a trap 9.4 g of n-butylmercaptan was collected.

o-Tolylamino (diethylamino) borane. In a manner similar to the preceding experiment 7.7 g of o-tolylamino (diethylamino) borane was obtained from 11.5 g of n-butylmercapto(diethylamino) borane and 8.0 g of o-toluidine.

B.p. 87-89° at 1.5 mm.  $d_4^{20}$  0.9145,  $n_D^{20}$  1.5228.

Found %: C 69.84; H 10.14; B 5.99. M 181.7.  $C_{11}H_{19}N_2B$ . Calculated %: C 69.49; H 10.07; B 5.69. M 190.1.

Bis(phenylamino) borane. A mixture of 6.0 g of phenylamino(diethyl amino) borane and 3.2 g of aniline was heated at 60-80°C and a pressure of 100 mm for 1.5 hours, thus distilling off the diethyl amine which was evolved. In a trap 1.2 g of diethyl amine was collected. The residue in the flask, which crystallized upon cooling, was carefully washed with hexane. Yield 4.2 g (63%) of bis(phenylamino)borane with m.p. 103-110°C (decomp.). After crystallization from hexane the melting point of the bis(phenylamino) borane was not raised.

Found %: C 73.18; H 7.04; B 5.37, M. 200.8.  $C_{12}H_{13}N_2B$ . Calculated %: C 73.48; H 6.68; B 5.52; M 196.1.

Bis(phenylamino) borane formed needle-shaped crystals, soluble in benzene and ether. It reacted violently with alcohol with the evolution of hydrogen.

Bis(diethylamino) borane. In the apparatus described above for the synthesis of ethylmercapto(diethylamino) borane was placed 10.0 g of diethyl amine- borane and 9.5 g of diethyl amine was added dropwise at 130-140°C over the course of 12 hours. By fractional distillation a fraction was obtained with b.p. 26-29°C at 1.5 mm. On repeated distillation 10.5 g (58 %) of bis(diethylamino)borane was obtained.

B. p. 62-64°C at 16 mm,  $d_4^{20}$  0.7870,  $n_D^{20}$  1.4330.

Found %: C 61.59; H 13.93, M 148.6.  $C_8H_{21}N_2B$ . Calculated %C61.55; H 13.56. M 156.1.

Action of Diethyl Amine on Butylmercapto(diethylamino) Borane. a) A mixture of 6.3 g of butylmercapto (diethylamino) borane and 2.9 g of diethyl amine was boiled for 5 hours (temperature of mixture 100-110°C). Upon distillation 3.0 g (53%) of bis (diethylamino) borane was obtained with b.p. 29-34°C at 2 mm,  $n_D^{20}$  1.4336, and 3.0 g (47%) of unreacted butylmercapto(diethylamino) borane was recovered with b.p. 48-51 at 1.5 mm. b) By boiling a mixture of 5.1 g of butylmercapto(diethylamino)borane and 2.4 g of diethyl amine for 10 hours, 2.4 g (52 %) of bis(diethylamino)borane was obtained with b.p. 30-35°C at 2 mm, and 2.5 g of butylmercapto(diethylamino) borane was recovered with b.p. 50-55°C at 2 mm.

Action of Butylmercaptan on Bis(diethylamino) borane. A mixture of 4.9 g of bis(diethylamino) borane and 4.2 of butylmercaptan was boiled for 3.5 hours (temperature of mixture 100-110°C). By fractional distillation 2.0 g (40 %) of unreacted bis(diethylamino) borane with b.p. 32-36°C at 2 mm and 2.3 g (43%) of n-butylmercapto(diethylamino) borane with b.p. 44-46°C at 1 mm,  $n_D^{20}$  1.4640, were obtained.

Action of n-butylmercaptan on ethylmercapto (diethylamino) borane. In a Claissen flask were placed 4.6 g of ethylmercapto(diethylamino) borane and 4.2 g of n-butylmercaptan. The mixture was heated, thus gradually distilling off ethyl mercaptan. Upon distillation of the residue 5.0 g of butylmercapto(diethylamino) borane was obtained with b.p. 52-54°C at 2 mm. Yield 91%.

Bis(N-methyl-N-phenylamino) borane. a) To a mixture of 12.7 g of n-butylmercapto(diethylamino) borane was added dropwise at 0°C, with stirring, 7.8 g of methylaniline. Then the volatile reaction products were distilled off in vacuum by slight heating. The residue was subjected to fractional distillation. The following fractions were obtained: 1) a fraction with b.p. 52-70°C at 1.5 mm, containing unreacted n-butylmercapto(diethylamino)-borane in the amount of 5.1 g; and 2) a fraction distilling at 124-129°C at 1.5 mm in the amount of 5.9 g, which was bis (N-methyl-N-phenylamino)- borane. The yield of the latter was 42%. The compound was redistilled once again.

B. p. 125-128°C at 1.5 mm,  $d_4^{20}$  1.033,  $n_D^{20}$  1.6035.

Found %: C 75.20; H 7.61, M 212.4.  $C_{14}H_{17}N_2B$ . Calculated %: C 75.02; H 7.65. M 224.1.

b) A mixture of 6.7 g of n-butylmercapto(diethylamino) borane and 9.0 g of methylaniline was heated in a Claissen flask at 20 mm, thus distilling off the n-butylmercaptan and diethyl amine that were given off. Upon distillation of the residue 7.2 g of bis (N-methyl-N-phenylamino) borane was obtained with b.p. 124-127°C at 1.5 mm. Yield 83%.



#### SUMMARY

1. The action of mercaptans on diethyl amine-borane has produced alkylmercapto(diethylamino) boranes, a previously unknown type of boron compound.
2. The action of amines on alkylmercapto(diethylamino) boranes has produced N-substituted diaminoboranes, among them unsymmetrical diethylamino (arylamino) boranes.
3. Upon heating alkylmercapto(diethylamino) boranes with higher mercaptans, exchange of the alkylmercapto groups occurred.
4. In alkylmercapto(diethylamino) boranes the alkylmercapto and diethylamino groups were more reactive than the hydrogen on the boron atom.

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SYNTHESIS OF DIPHENYL-*p*-ALLYLPHENYLSTIBINE AND CHEMICAL  
PROPERTIES OF TERTIARY STIBINES OF THE TYPE  $(C_6H_5)_2SbC_6H_4X$ ,  
WHERE X IS A NUCLEUS SUBSTITUENT

F. Yu. Yusunov and Z. M. Manulkin

Tashkent Pharmaceutical Institute

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In the chemistry of aromatic elementoorganic compounds, attention of researchers has been drawn to studies of the effect of substituents in the benzene nucleus on the physicochemical properties of organometallic substances. Among organoantimony compounds the mixed aromatic tertiary stibines are little known, especially when substituted in the aromatic ring. We decided to fill in the gap somewhat. Our problem was to clarify the effect of a substituent on the physical and chemical properties of an organoantimony compound.

The following new organoantimony compounds had been prepared by us [1] earlier for that purpose: diphenyl-*o*-tolylstibine, diphenyl-1,3,5-xylylstibine, diphenylcyclohexylphenylstibine, diphenyl-*p*-anisylstibine, diphenyl-*p*-phenetylstibine, and diphenyl-*p*-phenoxyphenylstibine; for those we determined a number of physical constants.

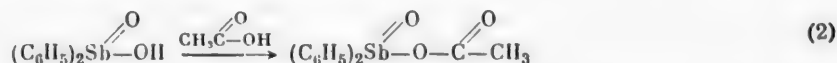
The synthesis of another new product—diphenyl-*p*-allylphenylstibine—is discussed here. The reaction proceeded according to the scheme:



The formula of the product obtained was proved by analysis for antimony and by parachor measurements [2]. Thus a mixed aromatic organometallic antimony compound with an allyl radical in the benzene ring was synthesized for the first time.

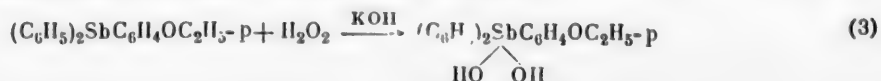
The research was also devoted to the study of some chemical conversions of the new substances mentioned above, of the type  $(C_6H_5)_2SbC_6H_4X$ , and to the preparation of a number of their derivatives so far undescribed in the literature. The chemical research [2] was directed toward elucidation of the oxidation process (Expts. 2-6), addition of bromine and hydroxyls to the unsaturated antimony atom and to the double bond of the allyl radical (Expts. 7-12), and also in part toward the decylation process, Expt. 13).

After standing in air for one week, the stibines in question showed no oxidation or regrouping of the radicals—symmetrization (Expt. 2). After one month, diphenyl-*o*-tolylstibine, diphenyl-*p*-allylphenylstibine, and diphenyl-*p*-cyclohexylphenylstibine became turbid. The product was diphenylstibinic acid (Expts. 3,4,5). The latter was converted to the acetate derivative (Expt. 6); the process goes by the scheme:



The addition of hydroxyl groups and of bromine was studied with diphenyl-*p*-phenetylstibine, diphenyl-*p*-bromophenylstibine, and diphenyl-*p*-allylphenylstibine.

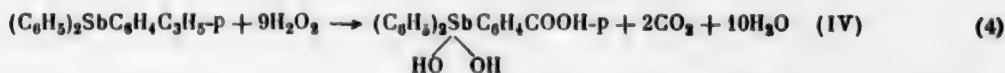
When diphenyl-*p*-phenetylstibine was shaken with 3% hydrogen peroxide solution in an alkaline medium, the dihydroxide of diphenyl-*p*-phenetylantimony (Expt. 7) was obtained as follows:



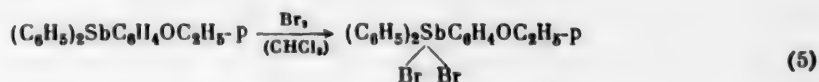
The dihydroxide of diphenyl-*p*-bromophenylantimony was prepared analogously.  $(C_6H_5)_2SbC_6H_4Br-p$  (Expt. 8).



In the case of diphenyl-*p*-allylphenylstibine, the dihydroxide of diphenyl-*p*-carboxyphenylantimony (Expt. 9) was formed instead of the expected tetrahydroxyl derivative. Probable reaction course:



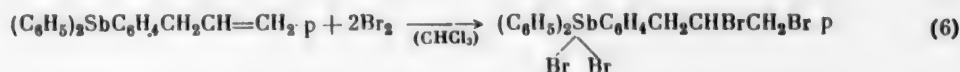
When bromine was added to diphenyl-*p*-phenethylstibine in a chloroform medium, the dibromide of diphenyl-*p*-phenethylantimony (Expt. 10) was obtained:



The dibromide of diphenyl-*p*-bromophenylantimony was obtained analogously.  $(C_6H_5)_2SbC_6H_4Br-p$  (Expt. 11)

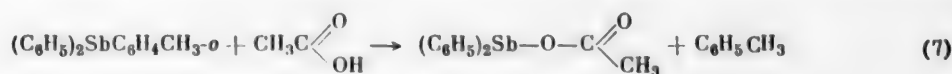


When bromine reacted with diphenyl-*p*-allylphenylstibine, the product was the dibromide of diphenyl-*p*-(2,3-dibromopropyl)phenylantimony (Expt. 12); evidently the reaction proceeds as:



The hydroxyl and bromine derivatives obtained are mainly solid substances with a definite melting point and soluble in organic solvents. Their structure was proved by analysis for antimony (Expts. 7-12).

Dearylation was studied on diphenyl-*o*-tolylstibine by boiling with an excess of glacial acetic acid (Expt. 13):



The resulting substance was characterized by mixed melting point test with a known compound, and proved by analysis for antimony.

Results of chemical conversions of compounds such as  $(C_6H_5)_2SbC_6H_4X$  can be summarized as follows:

It is probable that atmospheric oxygen brings about oxidation in a month's period, which process is accompanied by dearylation. The oxidation product is diphenylstibinic acid  $(C_6H_5)_2SbOOH$ .

Dearylation does not occur upon action of hydrogen peroxide in alkaline medium, nor on bromination in a chloroform medium; in that case addition of the respective hydroxyl or bromine to the unsaturated antimony atom takes place.

When diphenyl-*p*-allylphenylstibine is brominated, bromine is added at the double bond of the allyl radical; hydrogen peroxide effects the addition of hydroxyls only to the antimony atom, but in place of the allyl radical a carboxyl group forms in the benzene ring.

The splitting off of an *o*-tolyl radical before a phenyl radical agrees with the series of relative electronegativities of radicals according to Kharasch [3], elaborated by A. N. Nesmeyanov and K. A. Kocheshkov [4].

#### EXPERIMENTAL

**Expt. 1. Synthesis of Diphenyl-*p*-allylphenylstibine.** The Grignard reagent was prepared in the usual manner from 11.8 g *p*-bromoallylbenzene and 1.7 g magnesium in 50 ml absolute ether. The brown liquid thus obtained was cooled, and to it added, in small portions and over a period of 30 minutes with constant mechanical agitation,

9.3 g diphenylstibine chloride dissolved in 20 ml absolute ether. After heating for 1.5 hours on a steam bath, the mixture cleared up and turned yellow. Then the reaction mass was decomposed with water. The ether layer was separated and dried over calcium chloride. After removal of the ether, the residue was vacuum distilled. The lower fraction (3.6 g) boiled at 75°C (3 mm); it was distilled at 153-154°C (normal pressure), contained no halogen, burned completely, which facts correspond to allylbenzene [5]. The main fraction distilled at 205-210°C (3 mm) and was a yellow oily liquid with a specific odor. Yield: 7.4 g (62%). The substance burned, leaving a dull deposit, and contained no halogen:

$d_4^{25}$  1.2891,  $n_D^{25}$  1.6300,  $\sigma_{35}$  30.60 erg/cm<sup>2</sup>, [P] 721.1, calc. 742.0;  $MR_D$  108.40, calculated without antimony 89.20, hence  $AR_{Sb}$  = 19.20.

Found %: Sb 30.65, 30.76 (iodometrically)[b].  $C_{21}H_{19}Sb$ . Calculated %: Sb 31.04.

Expt. 2. Stability of compounds in question on standing in air for one week. Stibines prepared earlier [1] and during this research were left in small quantities in air for observation. No visible changes were noted after one week.

Expt. 3. Oxidation of diphenyl-o-tolylstibine on standing in air for one month. Part of the substance stood in air for one month. After that time a thick mass of a solid substance formed, which then was treated twice with ether, alcohol, chloroform, and benzene. The amorphous compound insoluble in the named solvents, melted at 286°C, burned, and contained antimony. In the literature, diphenylstibinic acid has a melting point of 287°C [7]. Free iodine is formed when the product in acid medium is treated with potassium iodide.

Expt. 4. Oxidation of diphenyl-p-allylphenylstibine on standing in air for one month. When diphenyl-p-allylphenylstibine stood in air for one month, it congealed to a whitish, gelatinous mass; two layers formed on heating to 50°C. The upper, mobile layer turned out to be the starting material. The lower layer was an amorphous powder difficultly soluble in organic solvents. After treatment with the solvents, the product melted at 285-286°C, which corresponded with the melting point of diphenylstibinic acid [7]. A mixed melting point test with diphenylstibinic acid prepared in Expt. 3 gave no melting point depression.

Found %: Sb 39.76, 39.68.  $C_{12}H_{11}O_2Sb$ . Calculated %: Sb 39.49.

Expt. 5. Oxidation of diphenyl-p-cyclohexylphenylstibine on standing in air for one month. Diphenyl-p-cyclohexylphenylstibine was allowed to stand in air for one month. As a result a gelatinous layer formed on the bottom and surface of the substance, while its middle part remained unchanged. The latter was carefully decanted (its composition could not be determined), and the rest treated with ether. The ether suspension was centrifuged, the residue washed with ether and dried. The amorphous powder thus obtained melted at 286°C [7] and did not dissolve in organic solvents. A mixed melting point test with diphenylstibinic acid gave no melting point depression.

Expt. 6. Effect of glacial acetic acid on diphenylstibinic acid. The amorphous powder (diphenylstibinic acid) obtained in experiments 3, 4, and 5, was all collected. One g of that substance was dissolved in 20 ml glacial acetic acid, and digested for 20 minutes. After cooling, a large amount of water was added to it, and a precipitate formed.

The latter was dissolved in an excess of acetone; partial spontaneous evaporation of the solvent precipitated adhering clusters of needle-like crystals, melting at 159-160°C (Equation II). They readily dissolved in chloroform and glacial acetic acid; they were insoluble in water. A mixed melting point test with known diphenylstibine acetate- $C_6H_5)_2SbOCOCH_3$ - showed a large depression.

Found %: Sb 34.45, 34.43.  $C_{14}H_{13}O_3Sb$ . Calculated %: Sb 34.76.

Expt. 7. Effect of hydrogen peroxide solution in alkaline medium on diphenyl-p-phenetylstibine. Two g diphenyl-p-phenetylstibine was treated under vigorous agitation for one hour with 15 ml of 4% hydrogen peroxide in the presence of 8 ml 1N KOH. The resulting clear water layer was decanted from a solid white mass adhering to the walls of the flask. The mass was washed with water, and dried, melting at 136-138°C. After purification with a small quantity of ether and benzene, crystals melting at 140-141°C were obtained.

The dihydroxide of diphenyl-p-phenetylantimony readily dissolved in acetone and very sparingly in water.

Found %: Sb 28.01, 28.14.  $C_{20}H_{21}O_3Sb$ . Calculated %: Sb 28.31.

Expt. 8. Effect of hydrogen peroxide solution in alkaline medium on diphenyl-p-bromophenylstibine. One of the substance was treated with 10 ml of 3% hydrogen peroxide and 7 ml of 1 N KOH solution, and the main mass adhered to the walls of the flask. The aqueous layer was separated by filtration. The sediment remaining on the

filter and the walls of the flask was washed with water, and then with ether. The dried white powder melted at 133-134°C.

The dihydroxide of diphenyl-p-bromophenylantimony readily dissolved in acetone and chloroform, and sparingly in alcohol and water.

Found %: Sb 25.99, 25.84.  $C_{18}H_{16}O_2BrSb$ . Calculated %: Sb 26.18.

Expt. 9. Effect of hydrogen peroxide solution in alkaline medium on diphenyl-p-allylphenylstibine. One g of diphenyl-p-allylphenylstibine was treated with 40 ml of a 3% hydrogen peroxide solution and 15 ml of a 1 N KOH solution. Then the mixture was filtered from the small quantity of a suspension. The filtrate was treated with an excess of 0.5 N hydrochloric acid. Abundant flakes precipitated, which were suctioned off and washed several times with water, upon which they turned out to be a lemon-yellow powder decomposing at 166-173°C (evidently by a process of decarboxylation).

Found %: Sb 28.44, 28.20.  $C_{19}H_{17}O_4Sb$ . Calculated %: Sb 28.31.

Analysis for COOH. 0.4018g substance: Used 10.3 ml, 0.0832 N NaOH which corresponds to 0.3684 g (91.7%)  $(C_6H_5)_2SbC_6H_4COOH \cdot P$ .



Expt. 10. Effect of chloroform solution of bromine on diphenyl-p-phenetylstibine. To 0.5 g of diphenyl-p-phenetylstibine dissolved in 10 ml chloroform was added dropwise a 10% chloroform solution of bromine to a persistent rose-yellow color, after which the mass was allowed to stand for two hours. The solvent was then removed, and a thick, oily residue was obtained, from which crystals in the form of leaflets, and melting at 212-213°C, were isolated by treatment with an ether-acetone mixture. Slow recrystallization from acetone yielded rhombic crystals melting at 213°C. The dibromide of diphenyl-p-phenetylantimony is very soluble in chloroform, benzene, and insoluble in alcohol, petroleum ether, and water.

Found %: Sb 21.04, 20.84.  $C_{20}H_{19}OBr_2Sb$ . Calculated %: Sb 21.14.

Expt. 11. Effect of bromine on diphenyl-p-bromophenylstibine. To one g of diphenyl-p-bromophenylstibine dissolved in 10 ml chloroform was added dropwise a 10% chloroform bromine solution to a persistent yellow color. The mixture was allowed to stand over night, and the solvent removed. The remaining thick oil was then treated with small quantities of ether and alcohol, upon which white, needle-like crystals melting at 200-201°C, formed. The dibromide of diphenyl-p-bromophenylantimony readily dissolved in acetone, benzene, ethyl acetate, and was insoluble in water.

Found %: Sb 20.85, 20.76.  $C_{18}H_{14}Br_2Sb$ . Calculated %: Sb 20.64.

Expt. 12. Effect of bromine on diphenyl-p-allylphenylstibine. Same experimental conditions. After removal of the solvent, the residue obtained was treated with alcohol or petroleum ether. A granular powder melting at 224-225°C was obtained. The dibromide of diphenyl-p-2, 3-dibromopropylphenylantimony readily dissolved in benzene, chloroform, and sparingly in alcohol and petroleum ether.

Found %: Sb 17.00, 16.83.  $C_{21}H_{19}Br_4Sb$ . Calculated %: Sb 17.11.

Expt. 13. Dearylation of diphenyl-o-tolylstibine. To 0.5 g of diphenyl-o-tolylstibine was added 10 ml glacial acetic acid; the mixture was digested for 30 minutes. Water was added to the cooled solution; the solid product was isolated, washed with water, and dried. After two recrystallizations from ligroin, crystals melting at 133°C were obtained. A mixed melting point test with known diphenylstibine acetate gave no depression.

Found %: Sb 36.04, 36.15.  $C_{14}H_{13}O_2Sb$ . Calculated %: Sb 36.42.

#### CONCLUSIONS

1. Diphenyl-p-allylphenylstibine was synthesized for the first time.
2. Tertiary stibines of the type  $(C_6H_5)_2SbC_6H_4X$  were characterized chemically. The process of air oxidation was studied; additions of bromine and hydroxyls at the unsaturated antimony atom and the allyl radical double bond were studied, and the process of dearylation was partially demonstrated.
3. A number of new organometallic antimony compounds was synthesized.

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# REACTION MECHANISM STUDIES ON THE DISPROPORTIONATION OF HEXAETHYLDISTANNANE

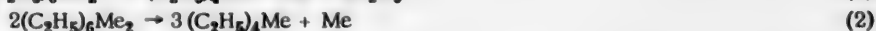
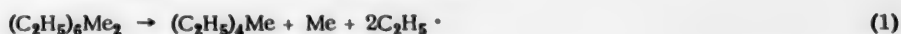
G. A. Razuvaev, N. S. Vyazankin, and O. A. Shchepetkova

Scientific Research Institute of Chemistry of the N. I. Lobachevski  
Gor'kov State University

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It was shown earlier, that thermal decomposition (1) must be strictly distinguished from disproportionation (2) in the cases of hexaethyldiplumbane [1] and hexaethyldistannane [2].



Me = Pb and Sn.

It was found, that reaction (2) is catalytic and can be brought about by very small amounts (2-3 weight-%) of some compounds. In particular, it is catalyzed by metallic chlorides similar to  $AlCl_3$ , mixed organometallic compounds such as  $(C_2H_5)_3PbCl$ , and other substances [3] which initiate the redistribution of radicals in organometallic compounds.

In order to elucidate the mechanism of disproportionation the manner of decomposition of symmetrical tetraethyldichlorodistannane [4] made an interesting study, since that compound has the metal-metal bond and at the same time should exhibit properties of mixed organometallic compounds, in particular, to initiate reaction (2).

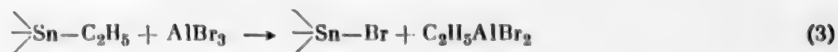
The investigation showed (Table 2, Expt. 1), that in that case the thermal decomposition changes to a complicated oxidation-reduction process which is not accompanied by formation of gaseous products and free metal. Evidently this process has much in common with reactions of radicals rearrangements, since addition of a catalyst as strong as  $AlCl_3$  (Expt. 2) is not evidenced by the nature of decomposition products and does not essentially change their ratios.

Tetraethyldichlorodistannane, instead, is a very weak catalyst for reaction (2), if at all; its addition (2-3 weight-%) does not initiate disproportionation of hexaethyldistannane under rather severe conditions (180-190°C).

The given fact and the absence of metallic tin among the products of thermal decomposition allow one to assert, that compounds of the type of tetraethyldichlorodistannane cannot be the primary products of a reaction between hexaethyldistannane with catalysts during the disproportionation according to reaction (2).

To prove this assumption, we studied the reaction of hexaethyldistannane with equimolar quantities of aluminum bromide in a medium of dry benzene (Expt. 3). In that case the atomic ratio halogen: tin in the reaction mixture was greater than in tetraethyldichlorodistannane. The reaction nevertheless produced free metal. No brominated compounds with a metal-to-metal bond were found among the products. The yield of metallic tin agreed well with the one calculated on the basis of reaction (2). The reaction proceeded with the formation of intermediate unstable, intensely cherry red colored compounds, which is known to be characteristic of disproportionation of  $(C_2H_5)_6Sn_2$  by the effect of catalytic quantities of an aluminum halide [5].

In contrast to reaction (2), however, the organotin product of the reaction between  $(C_2H_5)_6Sn_2$  and  $AlBr_3$  is not tetraethyltin, but a mixture of triethyltin bromide and diethyltin tribromide. As a consequence the dealkylation reaction, studied in detail by Manulkin [6], begins to play a conspicuous role in the process in question.



All this indicates, that when hexaethyldistannane is heated with an equimolar quantity of  $\text{SnCl}_4$  (see Expt. 4), the yield of metallic tin is as high as 13.7% of total metal used in the reaction, or 20.6% of tin contained in the hexaethyldistannane charge. If the reaction proceeded strictly according to reaction (2) (which is the case when  $\text{SnCl}_4$  is taken in catalytic quantities), the yield of tin would be 25.0% of metal contained in  $(\text{C}_2\text{H}_5)_6\text{Sn}_2$ .

No. of expt.	Used for reaction (Charge)		Temperature	Time (hr)	Yield of products (in % by tin*)				
	(in moles)	Benzene (in ml)			$\text{SnCl}_2$	$(\text{C}_2\text{H}_5)_3\text{SnCl}$	$(\text{C}_2\text{H}_5)_2\text{SnCl}$	$(\text{C}_2\text{H}_5)_4\text{Sn}$	Sn
1	0.0024 $(\text{C}_2\text{H}_5)_4\text{Sn}_2\text{Cl}_2$	—	190—230°	3.5	30.9	10.9	22.0	36.2	0.0
2	0.0047 $(\text{C}_2\text{H}_5)_4\text{Sn}_2\text{Cl}_2$ ; 0.0022 $\text{AlCl}_3$	—	190—230	5.5	23.5	25.8	24.9	25.8	0.0
3	0.0060 $(\text{C}_2\text{H}_5)_6\text{Sn}_2$ ; 0.0060 $\text{AlBr}_3$	15	100	2.5	0.0	18.1	43.4	—	26.0
4	0.0050 $(\text{C}_2\text{H}_5)_6\text{Sn}_2$ ; 0.0050 $\text{SnCl}_4$	11	100	6	0.0	45.1	39.8	0.0	13.7
5	0.0103 $(\text{C}_2\text{H}_5)_6\text{Sn}_2$ ; 0.0103 $\text{SnCl}_4$	11	70	2	24.2	31.1	17.5	26.8	0.0
6	0.0063 $(\text{C}_2\text{H}_5)_6\text{Sn}_2$ ; 0.0063 $\text{SnCl}_2$	10	115	4	18.2	6.0	18.5	33.3	24.0

\* Assumed as 100 % that quantity of tin used in the reaction mixture with all components.

It seems to us that the insignificant lowering in the yield of tin as opposed to that obtained by reaction (2) indicates an interaction of  $(\text{C}_2\text{H}_5)_6\text{Sn}_2$  with equimolar quantities of  $\text{SnCl}_4$  without intermediate formation of compounds similar to tetraethyldichlorodistannane.

Stannous chloride should also be counted among the intermediates of the reaction in question; it can be obtained in sufficiently high yield when the process is conducted under mild temperature conditions (Expt. 5). It is interesting to note, that in the latter case no free metal is found in the reaction mixture.

In order to elucidate the role of stannous chloride in the disproportionation process, it was interesting to study its reaction with hexaethyldistannane. Thus it was established that anhydrous stannous chloride, even in an absolute alcohol medium in which it is practically insoluble, reacts vigorously with hexaethyldistannane (Expt. 6). There the yield of elemental tin is 24.0% of metal present in the reaction mixture, or 36.1% of metal present in hexaethyldistannane. Such a high yield of tin evidently can be explained by the fact that stannous chloride not only catalyzes the disproportionation of hexaethyldistannane, but also manifests its reducing properties.

Equimolar quantities of stannous chloride and hexaethyldistannane in anhydrous acetone behave quite differently. In that case the main product is a powderish, intensely brick colored, amorphous mass slightly soluble in acetone, and we think it is an organotin polymer. The product obtained reacts vigorously (with heating up) with atmospheric oxygen and forms a colorless, infusible powder.

We noted the formation of polymeric organotin compounds during the disproportionation of hexaethyldistannane earlier. In particular, when reaction (2) was conducted under mild temperature conditions (achieved by heating  $(\text{C}_2\text{H}_5)_6\text{Sn}_2$  with catalytic quantities of aluminum chloride to 70°C), the product was a thin, cherry red polymer, which further decomposed to free metal and tetraethyltin [5]. The assumption was made that the basis of such a polymer type are long branched chains of tin atoms. To prove this assumption, it was expedient to study the reaction of polymeric compounds with benzoyl peroxide.\*

We had shown earlier [7] that hexaethyldistannane under very mild conditions reacts with benzoyl peroxide with cleavage of the metal-metal bond.



Contrarily, reaction of benzoyl peroxide with organotin compounds which have no Sn-Sn bond proceeds sluggishly and only at elevated temperatures, and is accompanied by the formation of carbon dioxide and a complex mixture of gaseous hydrocarbons [8].

\* Previous communication, see [9].

Investigation showed, that organotin polymers characteristically react very easily with benzoyl peroxide solutions in benzene free of atmospheric oxygen. The reactions take place at room temperature after 3-5 hours without any evolution of CO<sub>2</sub> or gaseous hydrocarbons. It seems to us that this fact indicates the presence of tin-tin bonds in the polymer. In addition, it also indicates the absence of side processes and lets one assume that only Sn-Sn bonds in the polymer and O-O bonds in the peroxide cleave during the reaction. The reaction evidently proceeds without the formation of kinetically independent radicals in the reaction complex.

The reaction of benzoyl peroxide with the polymer formed during disproportionation of hexaethyldistannane according to equation (2) and under the effect of catalytic additions of anhydrous aluminum chloride [5] could be studied most thoroughly. Triethyltin benzoate, diethyltin dibenzoate, ethyltin tribenzoate, and metallic tin were found in the reaction mixture.

If the polymer under study were linear of the type  $(C_2H_5)_3Sn-Sn(C_2H_5)_2)_n-Sn(C_2H_5)_3$ , one would expect only the formation of triethyltin benzoate (at the expense of the primary metal atoms) and of diethyltin dibenzoate (at the expense of the secondary ones). The formation of ethyltin tribenzoate in this case seems unlikely for the following reasons. When the peroxide reacts with the polymer, no appreciable amounts of ethylene form, which indicates an absence of side processes (5) and (6).



We also established, that when an equimolar mixture of benzoyl peroxide and diethyltin dibenzoate is allowed to stand at room temperature for several days in a solution of dry benzene, no ethyltin tribenzoate forms. And finally, investigation showed that diethyltin dibenzoate is a very stable substance, is easily purified by vacuum distillation, and does not undergo disproportionation according to reaction (7), not even at elevated temperatures.



Consequently, the formation of appreciable quantities of ethyltin tribenzoate indicates the presence of tertiary metal atoms in the polymer under study. It was found from the ratios of quantities of reaction products, that 23.6% tin atoms in the polymer was primary, 19.9% secondary, and 27.6% tertiary. Also, 28.8% tin atoms was isolated from the polymer in the metallic state.

It is possible that metallic tin was formed at the expense of quaternary metal atoms in the polymer chain. The results obtained agree well with the previously developed ideas on the branched chain character in intermediates during the disproportionation reaction of hexaethyldistannane [2] and hexaethyldiplumbane [1].

#### EXPERIMENTAL

All experiments were done in sealed, evacuated ampoules. For the study of the reaction of hexaethyldistannane with metal halides (Table 1, Expts. 3-6) we used an apparatus made of two ampoules connected in the shape of the letter H. The starting material was put in and the contents of the ampoules were twice congealed and decongealed in vacuo in order to remove atmospheric oxygen. Then the ampoules were sealed and the reaction components mixed. The experimental results are given in Table 1. Some typical experiments are described below.

**Reaction of Hexaethyldistannane with Stannic Chloride at 100°C.** Hexaethyldistannane (5.58 g) in 10 ml dry benzene was mixed with a solution of 3.53 g SnCl<sub>4</sub> in 1 ml benzene, and kept thermostatically at 100°C over a period of six hours. When the ampule was opened, no gaseous hydrocarbons were discovered. The metallic tin (0.66 g) was filtered and washed with hot benzene. The benzene used for the washing of tin, was combined with the mother liquor. The mixture was concentrated on a steam bath, the residue dissolved in 5 ml hot hexane. On cooling, 3.79 g dichlorodiethyltin, m.p. 82°C, crystallized. A mixed melting point test with a pure substance gave no melting point depression.  $(C_2H_5)_2SnCl_2$  was separated from the mother liquor, the latter was diluted with ether and extracted with a 10% NaOH solution. Filtration of the alkaline layer gave 0.58 g of insoluble and infusible diethyltin oxide. The total yield, then, of dichlorodiethyltin was 4.54 g. To the ether solution was added 1.4 ml glacial acetic acid, and the mixture was allowed to evaporate at room temperature. This gave 1.58 g triethyltin acetate; melting point 133-134°C (from hexane). A mixed melting point test with known triethyltin acetate gave no depression.

A series of blank experiments established, that the yield of triethyltin acetate from triethyltin chloride by the given method was about 70%. Consequently, the content of triethyltin chloride in the reaction mixture was close to

3.91 g. It can be seen from data in Table 2, that the method described insures quantitative determination of the reaction products.

In Table 2, 100 % of tin, ethyl groups, and chlorine, is assumed to be that quantity introduced into the reaction with hexaethyldistannane and stannic chloride.

**Reaction of hexaethyldistannane with Stannic Chloride at 70°C.** Sections A and B of the apparatus pictured in Figure 1 were charged with 4.25 g hexaethyldistannane in 10 ml dry benzene and 2.70 g  $\text{SnCl}_4$  in 1 ml benzene. The apparatus was evacuated in the usual manner and sealed at D. The reaction components were mixed in section A and the mixture kept thermostatically at 70°C for two hours. Then the apparatus was turned over and the liquid portion of the reaction mixture was filtered over a dense glass filter E in section C, which was unsoldered at F. In a separately arranged experiment it was established, that additional thermostatic heating of the section C contents at 70 or 100°C for 20 hours did not lead to the formation of metallic tin. The sediment on filter E was washed several times with boiling, dry benzene. This gave 1.42 g of stannous chloride, melting point 246-247°C. The benzene extracts were combined with the contents of section C and analyzed by the method described in the previous experiment. The results are given in Table 3.

TABLE 2

Reaction products	Yield (in %)		
	by tin	by ethyl groups	by chlorine
0.66 g Sn	13.6	0.0	0.0
4.54 g $(\text{C}_2\text{H}_5)_2\text{SnCl}_2$	45.0	45.0	67.7
3.91 g $(\text{C}_2\text{H}_5)_3\text{SnCl}$	39.8	60.0	29.9
Total	98.4	105.0	97.6

TABLE 3

Reaction products	Yield (in%)		
	by tin	by ethyl groups	by chlorine
1.42 g $\text{SnCl}_2$	24.2	0.0	36.2
2.38 g $(\text{C}_2\text{H}_5)_2\text{SnCl}_2$	31.1	31.1	46.4
1.31 g $(\text{C}_2\text{H}_5)_3\text{SnCl}$	17.5	26.4	13.1
1.95 g $(\text{C}_2\text{H}_5)_4\text{Sn}$	26.8	39.8	0.0
Total	99.6	97.3	95.7

**Reaction of Hexaethyldistannane with Stannous Chloride in Absolute Acetone.** Hexaethyldistannane (2.33 g) in 2 ml acetone was mixed with a solution of 1.11 g  $\text{SnCl}_2$  in 15 ml acetone and kept thermostatically at 75°C for two hours. The reaction mixture turned light green, brick red, and finally, dark cherry red, in that order. Weight: 1.45 g. The residue was vigorously oxidized on contact with air, becoming a colorless, infusible mass. The sediment was separated, and the filtrate also decolorized on contact with air. By the usual method, 0.05 g diethyltin dichloride and 0.34 g triethyltin chloride was determined in the filtrate.

In a separate experiment, a calculated quantity of benzoyl peroxide dissolved in acetone was added to the reaction mixture which contained the polymer sediment, excluding atmospheric oxygen (see following experiment). Within a day and at room temperature, complete decolorization of the solution and solution of the polymeric sediment took place. After distillation of the acetone we obtained a crystalline mass, which readily dissolved in benzene and easily hydrolyzed to give benzoic acid. We were not able to isolate individual organotin substances from it.

**Reaction of Benzoyl Peroxide with the Polymer Formed During Disproportionation of Hexaethyldistannane [5].** Hexaethyldistannane (6.87 g) was mixed with 0.14 g (2.0 weight %) anhydrous aluminum chloride in the apparatus pictured in Figure 2, in section A; section B was charged with a solution of 4.04 g benzoyl peroxide in 20 ml dry

benzene. The apparatus was evacuated in the usual manner, and sealed at D. The contents of section A were kept thermostatically at 70°C until traces of metallic tin appeared in the polymeric mass which formed.

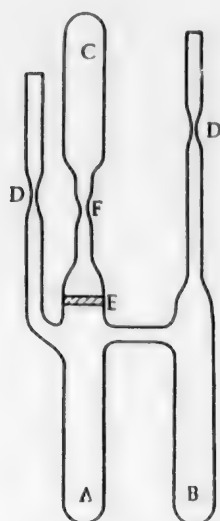


Fig. 1. (Explanation in text)

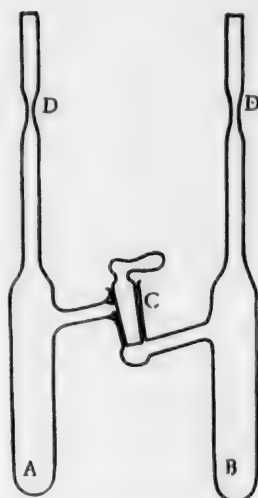


Fig. 2. (Explanation in text)

The mixture was cooled, the stopcock C opened, and the solution of peroxide was poured into section A. Gradual solution of the polymer then occurred, also decolorization of the solution and precipitation of a colorless, crystalline substance. Metallic tin was formed from the polymer during the process just described. After one day the crystalline precipitate became turbid from the metallic powder, and was filtered. The crystals were washed with three portions of dry, hot benzene. This gave 1.69 g ethyltin tribenzoate, m.p. 185-188°C (decomposition).

Found %: C 54.34; H 3.94; Sn 21.66.  $C_{25}H_{20}O_6Sn$ . Calculated %: C 54.05; H 3.95; Sn. 21.82.

The substance was slightly soluble in hot benzene, toluene, and methyl ethyl ketone. During attempts to recrystallize it from water-containing solvents, it hydrolyzed and split off benzoic acid. The metallic tin weighed 0.4 g, after washing with hot benzene and acetone.

The mother liquor was combined with the benzene extracts and the benzene was distilled off at reduced pressure; 2.43 g tetraethyltin contaminated with triethyltin chloride was also obtained; m.p. 175-190°C at 755 mm,  $n_D^{20}$  1.4790.

The remaining crystalline mass was transferred to a flask with a saber-like outlet tube, and purified from tarry products (0.8 g) by distillation. This gave a mixture of triethyltin benzoate and diethyltin dibenzoate, boiling at 130-168°C at 1 mm. Fractional crystallization from n-hexane yielded 0.99 g diethyltin dibenzoate melting at 120-123°C.

Found %: C 51.89; H 4.94; Sn 27.92.  $C_{18}H_{20}O_4Sn$ . Calculated %: C 51.59; H 4.81; Sn 28.32.

Triethyltin benzoate, which crystallizes poorly, (melting point of compound and of mixed test: 79-80°C) was converted to the triethyltin acetate for quantitative determination. For that purpose the mother liquors were treated with a 10% solution of NaOH. The hexane layer was removed, the aqueous layer extracted with ether. The organic layers were combined and acidified with 0.5 ml glacial  $CH_3COOH$ . Slow evaporation gave 0.90 g of crystalline triethyltin acetate, m. p. 131-133°C. A mixed melting point test with a pure substance gave no melting point depression. Thus, the reaction mixture contained 1.11 g triethyltin benzoate.

No ethane, ethylene, carbon dioxide, and ethyl benzoate was found among the reaction products.

Hydrolysis of ethyltin tribenzoate. Ethyltin tribenzoate (0.53 g) was digested for one hour in 10 ml dilute (1:1) hydrochloric acid. This gave 0.34 g benzoic acid. Yield: 89.5% of the theoretical. M.p. 122-123°C (from water).



Effect of benzoyl peroxide on diethyltin dibenzoate. Diethyltin dibenzoate (1.32 g) and 0.76 benzoyl peroxide (molar ratio 1:1) was dissolved in 7 ml dry benzene, and kept for 10 days at room temperature. The reaction mixture then yielded unchanged starting materials.

#### SUMMARY

1. It was shown, that symmetrical tetraethyldichlorodistannane is not the primary product in the reaction of catalysts which as  $\text{AlCl}_3$  with hexaethyldistannane during disproportionation according to the reaction  $2(\text{C}_2\text{H}_5)_6\text{Sn}_2 \rightarrow 3(\text{C}_2\text{H}_5)_4\text{Sn} + \text{Sn}$ .

2. The disproportionation of hexaethyldistannane in the presence of equimolar quantities of aluminum bromide, stannic chloride, and stannous chloride, was studied. The reaction products are metallic tin, triethyltin chloride, diethyltin dichloride, and tetraethyltin. Increasing the quantity of the catalyst little affects the yield of free metal. The reaction between hexaethyldistannane and  $\text{SnCl}_4$  proceeds via intermediate formation of stannous chloride.

3. The intermediate product in the disproportionation of hexaethyldistannane, under the action of  $\text{AlCl}_3$  and at moderate temperatures, is an organotin polymer with branched chains of metal atoms. The polymer readily reacts with benzoyl peroxide to form triethyltin benzoate, diethyltin dibenzoate, ethyltin tribenzoate, and metallic tin.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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## THE CHEMICAL SYNTHESIS OF 2-DEOXY- $\alpha$ -D-GLUCOSE 6-PHOSPHATE

A. L. Remizov

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In order to work out a biochemical method for determination of the activity of the enzyme hexokinase by rate of enzymatic phosphorylation of 2-deoxy-D-glucose we must have the 6-phosphate of this carbohydrate (II) in pure form. In the present communication we describe its chemical synthesis.

In the literature there is only a brief indication of the preparation of this compound by an enzymatic method [1,2]. There are also two descriptions of unsuccessful attempts to prepare it chemically [3, 21]. In distinction from this, detailed paths have been worked out in various ways for the chemical synthesis of 6-phosphates of glucose [4-8], galactose [12], glucosamine [9-11], and also the 6-phosphate of 2-deoxygalactose [13] and the 5-phosphate of 2-deoxyribose [14].

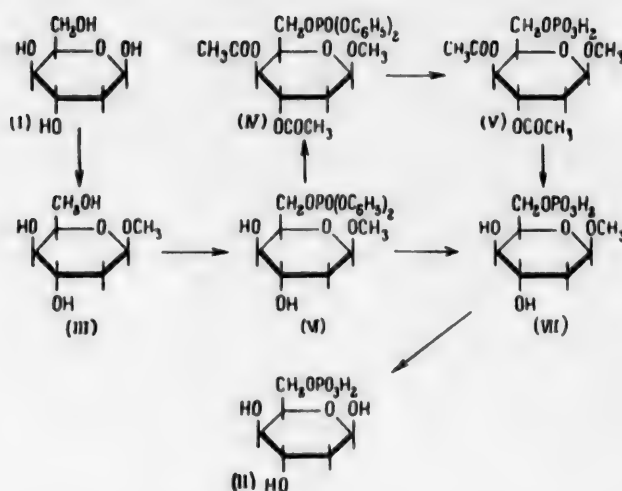
At the beginning of this work we tried to use for the phosphorylation of 2-deoxy-D-glucose (I) the method suggested for preparing 6-phosphates of glucose [5] and glucosamine [10-11]. For this we had to prepare the trityl (triphenylmethyl) derivative of the starting carbohydrate, acetylate it, isolate and separate the resulting mixture of anomers, remove the trityl group and phosphorylate the resulting acetylated product with a free hydroxyl group on the sixth carbon atom, later eliminating the protective group. However, after carrying out reaction of (I) with triphenylchloromethane under mild conditions and further acetylation, we could not isolate in the free state the expected triacetyl derivative of the trityl ether and prepare in pure form the detritylated product.

In order to avoid formation in the reaction of a mixture of the  $\alpha$ - and  $\beta$ -form, we undertook an analogous synthesis in which the starting 2-deoxyglucose was replaced by its methyl glucoside (III). However, the product obtained after reaction of (III) with trityl chloride and acetic anhydride was also nonhomogeneous and could not be purified. After preliminary removal of the trityl group it was converted to the diphenylphosphate (IV) from which by hydrolysis we obtained a very low yield of the 6-phosphate of 3,4-diacetyl-2-deoxy- $\alpha$ -methyl-D-glucopyranoside (V), isolated in the form of the bis-cyclohexylammonium salt and identified with the same salt obtained in another way, as described below.

Considerably better results were obtained by direct phosphorylation of the  $\alpha$ -form of methyl-2-deoxyglucopyranoside (III). As a result of carrying out the reaction under very mild conditions between (III) and diphenylchlorophosphate we obtained the sirupy 6-diphenylphosphate (VI) which after elimination of the phenyl group (by hydrogenolysis over Pt from  $\text{PtO}_2$ ) gave the 6-phosphate of 2-deoxy- $\alpha$ -methyl-D-glucopyranoside (VII), isolated in 50-55 % yield in the form of a very well crystallized bis-cyclohexylammonium salt.

Based on the possibility of obtaining its crystalline derivative, the diphenylphosphate (VI) was acetylated with acetic anhydride. However, the diacetate (IV) here isolated was also amorphous. It was dephenylated by hydrogenolysis and formed acid (V) which was converted into the cyclohexylammonium salt, identical with the salt obtained as described above in another way. This salt, after deacetylation in a medium of aqueous alcoholic alkali gave the 6-phosphate of methyl-2-deoxyglucoside (VII), identified in the form of its cyclohexylammonium salt, previously obtained from (VI).

In order to convert glucoside (VII) into the needed 2-deoxyglucose 6-phosphate (II), we heated the bis-cyclohexylammonium salt (VII) with an equivalent amount of 0.5 N HBr and the resulting acid (II) was converted to the barium salt which was precipitated by ethanol.



Compound (II) was very sensitive to alkali. In an attempt to isolate the pure neutral salt (it formed at pH above 9) we obtained a product with unsatisfactory analysis: high barium content and low in phosphorus. Since the formation of saccharic acid was excluded in this case because of the absence of hydroxyl in the 2-position in the carbohydrate molecule, we had to assume the possibility of a partial oxidation by oxygen of the air to the corresponding analog of gluconic acid, or a still more complex oxidative transformation.

On the other hand, isolation of the acid barium salt of (II) was accompanied by a great loss because of its high solubility. We were also unable to obtain crystalline salts with other bases, in this case, organic ones. Therefore the barium salt of this phosphate was isolated at pH no higher than 7.5. Under these conditions the neutral salt precipitated with a content, from the analytical data for Ba, of about 15 mole % of the acid salt.

The absence of phosphorus containing by-products in the resulting ester was demonstrated by chromatography (see experimental part).

To show the structure of the ester which was synthesized we carried out its oxidative splitting by periodic acid. We detected malonic aldehyde in the reaction product. Of the three possible esters of 2-deoxyglucose in this case, namely, the 3-, 4-, or 6-phosphate of 2-deoxyglucopyranose, only the last could give malonic aldehyde when split by periodic acid, so that its structure was shown.

When the present work had been completed, a report appeared of the analogous synthesis of 2-deoxyribose 5-phosphate [18].

#### EXPERIMENTAL

**2-Deoxy-α-methyl-D-glucoside 6-phosphate (VII).** To a solution of 0.89 g (5 mole) of 2-deoxy-α-methyl-D-glucoside (III) [15] in 7 ml of anhydrous pyridine we added in the course of 80-90 minutes a solution of 1.3 g (5.16 mole) of diphenylchlorophosphate in 8 ml of dry benzene. The reaction was carried out in an apparatus well protected from atmospheric moisture with mechanical stirring and continuous cooling in a bath with dry ice and alcohol at a temperature of minus 20-25°C. Stirring was continued for 1-2 hours at minus 5-0°C and the mixture was left over night at +5°C and then for 3-4 hours at room temperature. Then most of the solvent was distilled off in a vacuum through a trap with sulfuric acid; the residue was dissolved in 50 ml of chloroform, and the solution was freed from pyridine by shaking successively with a saturated solution of sodium chloride in 0.5 N H<sub>2</sub>SO<sub>4</sub> (in 5 ml portions until an acid reaction to Congo did not disappear in the water phase), with a solution of sodium bicarbonate (5 ml) and with a saturated solution of sodium sulfate (5 ml). The chloroform extract was dried over anhydrous MgSO<sub>4</sub> and evaporated in a vacuum; the residue was dissolved in 15 ml of anhydrous methanol, the solution was decolorized with charcoal and the solvent was distilled off in a vacuum. After drying in a vacuum over H<sub>2</sub>SO<sub>4</sub> a thick, colorless sirup remained (VI). Yield 1.4-1.6 g (70-80%). The product was dissolved in 25 ml of anhydrous methanol and the solution was boiled for 5-10 minutes with activated charcoal treated with nitric acid in order to remove catalyst poisons [19], and after filtration, was shaken in an atmosphere of hydrogen at room temperature and excess pressure of 0.2 atm

over 0.1 g of Pt from  $\text{PtO}_2$ ; the catalyst was replaced by fresh material\* when absorption of gas became sluggish. The reaction was complete after 8-10 hours. The amount of hydrogen used was 85-90% of the theory. The solution, separated from the catalyst, was made alkaline with a small excess of cyclohexylamine, and after cooling for an hour in an ice bath, a crystalline precipitate of the neutral cyclohexylammonium salt of (VII) came down and was filtered off and washed with anhydrous ethanol and ether. From the filtrate after evaporation in a vacuum and dilution with ether further portions of the salt precipitated. The total yield was 1.15-1.35 g (50-60% on the starting (III)). After recrystallization from hot 98% methanol, long needles with m.p. 216-218°C (decomposition)\*\*,  $[\alpha]_D^{22} + 42.8$  (c 8.0 in 0.01 M aqueous cyclohexylamine).

Found %: C 49.56, 49.40; H 9.22, 9.07; N 5.97, 6.05; P 6.91, 6.93.  $\text{C}_{19}\text{H}_{41}\text{O}_9\text{N}_2\text{P}$ . Calculated %: C 49.98; H 9.05; N 6.14; P 6.79.

**3, 4-Diacetyl-2-deoxy- $\alpha$ -methyl-D-glucoside 6-phosphate (V).** To the reaction mixture obtained from phosphorylation of 5 mole of (III) with diphenylchlorophosphate under the conditions described above we added twice the calculated amount of acetic anhydride (22 mmole) with mechanical stirring and cooling in an ice bath, over a period of 10-15 minutes. After keeping for 20 hours at room temperature in an apparatus protected from moisture the mixture was poured onto 25 g of ice and at a temperature not above 5°C was carefully neutralized with 25 ml of 4 N  $\text{H}_2\text{SO}_4$ . The reaction product was removed with ether (5 times with 10 ml), the ether extract was treated with 0.5 N  $\text{H}_2\text{SO}_4$  (twice with 5 ml), with a solution of  $\text{NaHCO}_3$  (twice with 5 ml), and with water (5 ml) and was dried over anhydrous  $\text{MgSO}_4$ . The solvent was distilled off in a vacuum, the residue was dissolved in anhydrous methanol (15 ml), the solution was filtered through a layer of charcoal, and the filtrate was evaporated dry in a vacuum. The resulting glassy mass did not crystallize after drying for many days in a vacuum over  $\text{P}_2\text{O}_5$ . Yield 2 g (83%).

For elimination of the phenyl groups, product (IV) was dissolved in 25 ml of anhydrous methanol and submitted to hydrogenolysis as in preparing (VII) (see above). After separation of the catalyst the solution was distilled off in a vacuum, and the residue was dissolved in 5 ml of hot isopropyl alcohol. After dilution with four times the volume of ether and cooling in an ice bath for 5-6 hours, a voluminous precipitate of bis-cyclohexylammonium salt of (V) came down. The yield of product after filtration, washing with ether, and air drying was 1.0-1.1 g (35-40%). After recrystallization from isopropyl alcohol with moist ether, long, tangled, fibrous crystals with m.p. 200-202°C (on plunging the capillary into an apparatus heated to 192-195°C). The substance melted without evident signs of decomposition, but the melting point depended on the length of heating.

The air dried salt, from the analytical data, contained  $1\frac{1}{2}$  molecules of water of crystallization, which was fully lost over KOH in a vacuum and quickly absorbed again in air.  $[\alpha]_D^{22} + 83.8$  (c 2.51, calculated on anhydrous substance in anhydrous ethanol).

Found %: C 48.45, 48.76; H 8.75, 8.95; N 4.78, 4.95; P 5.59, 5.62;  $\text{H}_2\text{O}$  4.84.  $\text{C}_{23}\text{H}_{45}\text{O}_{10}\text{N}_2\text{P} \cdot 1\frac{1}{2}\text{H}_2\text{O}$ .  
Calculated %: C 48.63; H 8.52; N 4.86; P 5.37;  $\text{H}_2\text{O}$  4.76.

**2-Deoxy- $\alpha$ -methyl-D-glucopyranoside 6-Phosphate (VII) from 3,4-diacetyl-2-deoxy- $\alpha$ -methyl-glucopyranoside 6-phosphate (V).** Deacetylation of (V) was carried out in a manner analogous to [13]. We dissolved 0.406 g (0.75 mmole) of neutral cyclohexylammonium salt of (V) in 12 ml of ethanol and made alkaline with 2.3 ml of 1 N NaOH. After 18 hours, the solution was diluted with 10 ml of water and passed through cationite SDB-3 in the cyclohexylammonium form. The eluate, free from sodium ions, was made alkaline with a small excess of cyclohexylamine and evaporated dry in a vacuum. After one recrystallization from anhydrous ethanol and then from 98% methanol we obtained 0.2 g (60%) of a preparation with m.p. 216-218°C (with decomposition) a mixed sample with the analogous salt obtained from (VI) as described above gave no melting point depression.

**Preparation of 3,4-diacetyl-2-deoxy- $\alpha$ -methyl-D-glucoside 6-phosphate (V) through the trityl derivative of 2-deoxy- $\alpha$ -methyl-D-glucoside.** To a solution of 0.89 g (5 mmole) of 2-deoxymethylglucoside (III) in 3 ml of anhydrous pyridine was added in the course of an hour at 0° with stirring mechanically a solution of 1.45 g (5.03 mmole) of triphenylchloromethane in 5 ml of anhydrous dioxane. After standing over night at +5°C and eight hour stirring at 18-20°C we added acetic anhydride (1.9 ml, 22 mmole) to the reaction mass. After 15 hours, the mixture was poured into 125 g of water with ice with simultaneous careful acidification with 2 N HCl to a weak acid reaction to litmus. The precipitate which solidified on stirring was filtered off, washed with water, and dried in a vacuum. Yield 2.55 g. M. p. 44-68°C. The substance was soluble in almost all organic solvents, from which it did not

\* It was found that a poisoned catalyst could not be cleaned. However, this lengthened the time of hydrogenation.

\*\* Here, as later, we give corrected melting points.

crystallize. For purification it was dissolved in ether, the solution was filtered and evaporated in a vacuum, the residue was again dissolved in methanol (10 ml) and the solution, decolorized with charcoal, was poured into 75 g of ice. After filtration and drying in a vacuum we obtained 2.06 g of substance with m.p. 50-70°C. According to the analysis, the preparation apparently contained an admixture richer in carbohydrate polytrityl derivatives.

Found %: C 72.5, 72.2; H 6.2, 6.3.  $C_{30}H_{32}O_7$ . Calculated %: 71.42; H 6.40.

To remove the trityl group a solution of 1.69 g of this product 20 ml of anhydrous ethanol was shaken in an atmosphere of hydrogen over 1.6 g of catalyst (5% Pd on charcoal [19] as in [14]. The solution, separated from the catalyst, was freed from alcohol by three evaporations in a vacuum with benzene and to the residue dissolved in 8 ml of anhydrous pyridine was added in the course of 10 minutes at 0°C a solution of 1.3 g (4.85 mmole) of diphenylchlorophosphate in 3 ml of dry benzene. After the solution stood at 18-20°C overnight, the solvent was distilled off in a vacuum, the mass was dissolved in 30 ml of ether, and the solution was shaken successively with 0.5 N  $H_2SO_4$ , with a solution of  $NaHCO_3$ , and with water. After drying over  $MgSO_4$ , the ether was distilled off and the residue was dissolved in 40 ml of boiling methanol, treated while boiling with activated charcoal, and after the solution had cooled and been filtered from the triphenylmethane which crystallized, it was shaken in an atmosphere of hydrogen over Pt from  $PtO_2$ . The filtrate, separated from the catalyst, was made alkaline with cyclohexylamine and after the corresponding treatment (see above) we obtained from it 0.5 g of impure product which after two crystallizations gave a product with m.p. 198-200°C (0.15 g). A mixed melting point with the bis-cyclohexylammonium salt of (V) obtained from (IV) as described previously gave no depression.

2-Deoxy- $\alpha$ -D-glucose 6-phosphate (II). Preparative experiments with polarimetric control showed that a solution of the cyclohexylammonium salt of (VII) in excess 0.1 N HBr acquired a constant angle of rotation after 30 minute heating on a boiling water bath. This time was taken as the optimum for carrying out the reaction for preparative purposes.

We dissolved 0.228 g (0.5 mmole) of the cyclohexylammonium salt of 2-deoxyglucose methyl glucoside 6-phosphate (VII) in 2.1 ml of 0.5 N HBr. The solution was heated for 30-40 minutes in a centrifuge tube (with a reflux condenser) on a boiling water bath, was made alkaline (after cooling) in an intense stream of nitrogen with good stirring, using 0.5 N  $Ba(OH)_2$  as accurately as possible to pH 7.5-7.6, but not more than 7.8 (test on brilliant yellow paper): it was freed from precipitating barium phosphate by centrifuging. The supernatant solution was decolorized by filtration through a bed of charcoal and diluted with five times its volume of ethanol to precipitate the Ba salt of (II), which, after standing for one hour in an ice bath, was separated by centrifuging, and washed (in the centrifuge tube) with ethanol and ether. Yield 1.8-1.9 g (85-90 %). For purification the salt was dissolved in 2 ml of water, the solution was filtered in a stream of nitrogen and diluted with 10 ml of anhydrous ethanol. The precipitate was separated as shown above. The salt which resulted under these conditions was a white powder, easily soluble in water, composed, according to analysis for Ba ion, of acid and neutral salt with considerable predominance of the latter. The ratio of the salts could vary depending on the pH at the moment of precipitation by alcohol.

The substance contained water of crystallization (apparently 2 moles per 1 mole of neutral salt) which was gradually lost in a vacuum over  $P_2O_5$ .

Found %: Ba 31.54, 31.45; P 7.81, 8.14;  $H_2O$  8.18.  $C_6H_{11}O_8PBa \cdot 2H_2O$ . Calculated %: Ba 33.07; P 7.47;  $H_2O$  8.67.

According to the analysis for Ba ion the content of neutral salt in the sample was 84.3 molar %.

An easily filtering crystalline preparation was obtained with a somewhat lower yield by precipitating it with ethanol from a water solution, acidifying with acid to a weak acid reaction to litmus (pH 6.2-6.4). According to the results of parallel potentiometric titration, of two samples by acid (titrating the neutral salt) and alkali (titrating the acid salt), the preparation contained 63% neutral and 37% acid salt.

The absence in this preparation of (II) of phosphorus-containing impurities was shown by chromatography on paper of type "M". of the Volodarskii Leningrad Works. At the starting line we placed a sample of orthophosphoric acid, 2-deoxyglucose 6-phosphate (II), and its methyl glucoside (VII). The solutions of the latter two substances had first been decationized with the cationite SDB-3. We used ascending chromatography in the system isopropyl alcohol-15% trichloroacetic acid (8:2). The chromatogram after development of the phosphate with molybdate [16] showed (see figure) that the preparation of (II) contained only traces of admixed phosphoric acid which was perhaps formed as a result of hydrolysis during the 12 hour chromatography.



Paper chromatography.

1) 2-Deoxy- $\alpha$ -methyl-D-glucoside 6-phosphate; 2) orthophosphoric acid; 3) 2-deoxy- $\alpha$ -D-glucose 6-phosphate.

Oxidation of 2-deoxyglucose 6-phosphate by periodic acid and determination in the reaction products of malonic aldehyde was carried out as follows [17, 20]. To 1 ml of  $10^{-4}$  M solution of the Ba salt of (II) was added 1 ml of 0.0125 M solution of periodic acid prepared in 0.125 N  $\text{H}_2\text{SO}_4$ . The total volume was brought to 4 ml with water and after 60 minute heating at  $40^\circ\text{C}$ , the excess oxidant was bound with 1 ml of arsenite solution (2 %  $\text{Na}_3\text{AsO}_3$  in 0.5 N HCl). We took a 1 ml sample from the solution and added to it 3 ml of 0.6% solution of sodium thiobarbiturate and after acidification by 1 N HCl to pH 2, the total volume was brought to 4.5 ml with water. The sample was heated in a tube with a ground glass stopper on a boiling water bath for 20 minutes. Then there appeared a rose color about equal in intensity to the color produced in an analogous sample which contained instead of the salt of (II) an equimolecular amount of 2-deoxyglucose.

#### SUMMARY

1. We have carried out for the first time the chemical synthesis of 2-deoxy-D-glucose 6-phosphate from 2-deoxy- $\alpha$ -methyl-D-glucoside.

2. During the synthesis we have obtained and characterized as the neutral cyclohexylammonium salts the previously undescribed 2-deoxy- $\alpha$ -methyl-D-glucoside 6-phosphate and 3,4-diacetyl-2-deoxy- $\alpha$ -methyl-D-glucoside-6-phosphate.

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# STUDIES IN THE ALLO- AND ISOALLOXAZINE SERIES

## VI. STUDIES OF THE SYNTHESIS OF QUINOXALINE, A POTENTIAL PRECURSOR OF ALLOXAZINES

V. M. Berezovskii and A. M. Yurkevich

All-Union Vitamin Research Institute

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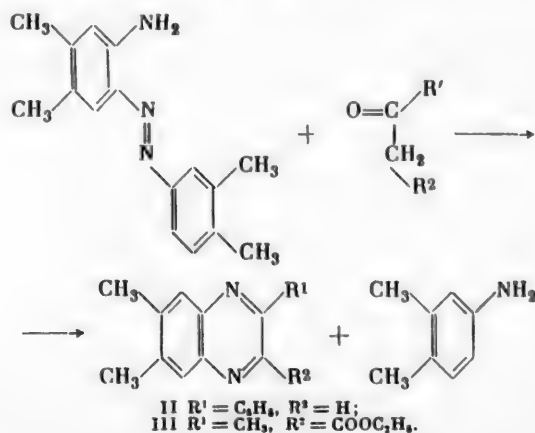
The condensation of primary and secondary orthoaminoazo compounds with barbituric acid is one of the most satisfactory reactions which permit preparation of isoalloxazines and alloxazines: riboflavin [1], and its stereoisomers [2,3], lumiflavin [4], lumichrome [5], and others. In the same way we have obtained in our laboratory thioriboflavin, thiolumichrome [6], and deoxyriboflavin [7].

In the present work we have studied the possibility of using the method of condensation of ortho-aminoazo compounds with carbonyl compounds which contain a mobile  $\alpha$ -hydrogen atom for preparing different substituted quinoxalines with the biologically important ortho-dimethyl system in the benzene ring; these are of interest as potential precursors of allo- and isoalloxazines.

Quinoxalines are usually obtained by condensation of o-phenylenediamine with derivatives of glyoxal or glyoxylic acid [8]. The small availability of the starting compounds, and also the nonhomogeneous character of the reaction leading in the case of ring-substituted derivatives of o-phenylenediamine to formation of isomeric quinoxalines, complicate the use of this method. Some quinoxalines can be obtained by the use of alkaline hydrolysis of isoalloxazines, for example, from riboflavin, 1,2-dihydro-6, 7-dimethyl-2-keto-1-D-ribitylquinoxalin-3-carboxylic acid, and from lumiflavin, the corresponding 1-methyl isomer [9].

Crippa has shown [10] that in the condensation of ortho-aminoazo dyes of the naphthalene series with ketones or  $\beta$ -ketoesters, there are formed naphthopyrazines. However, in the literature [11] there is evidence that o-aminoazobenzene gives quinoxaline in very small yield.

We condensed 3, 4-dimethyl-6-(3', 4'-dimethylphenylazo)-aminobenzene (I) with acetophenone and acetoacetic ester; as a result we obtained a good yield of 6, 7-dimethyl-2-phenylquinoxaline (II) and 2,6,7-trimethyl-3-carbethoxyquinoxaline (III) with characteristic absorption bands of quinoxalines in the ultraviolet spectra (see Fig. 1). It is interesting to note that both substances have very close absorption bands in the infrared spectra at  $1323$ - $1328$   $\text{cm}^{-1}$ , but there is not sufficient evidence to confirm that these bands are characteristic for quinoxalines. In the region of valence oscillation of the carbonyl group 2,6,7-trimethylquinoxaline (III) has a band with a frequency of  $1735$   $\text{cm}^{-1}$ , which is characteristic for  $> \text{C} = \text{O}$  in an ester group.





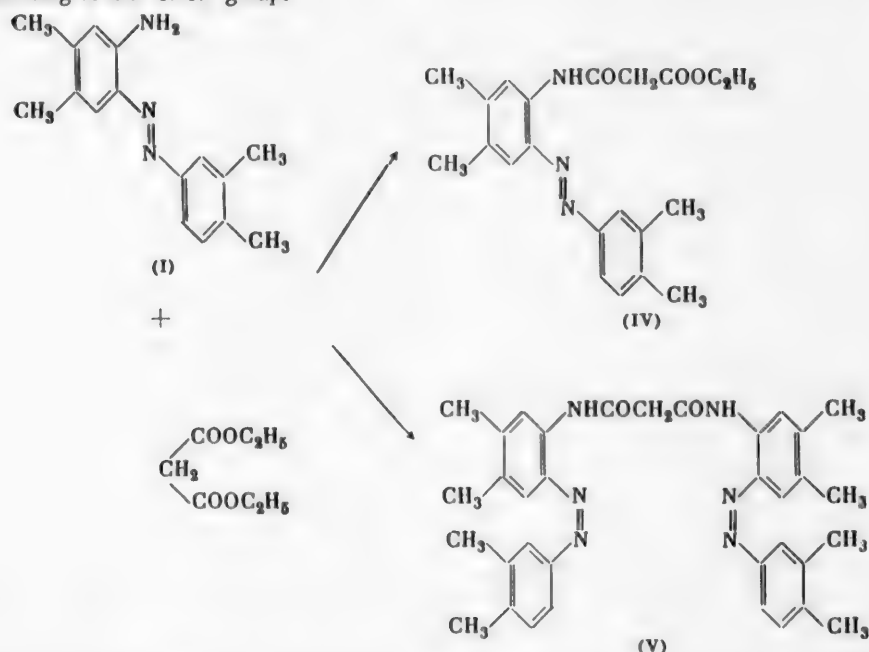
On condensation of ortho- aminoazo dyes with carbonyl compounds which contain a mobile  $\alpha$ -hydrogen atom there is splitting of the azo group with evolution of an aromatic amine; as a result, a quinoxaline is formed. We have showed that a catalyst for the reaction, besides hydrogen chloride, may be acetic and succinic acids.

We have studied the behavior in an analogous condensation of derivatives of malonic acid which contain an active hydrogen of the methylene group. Boiling of 3, 4-dimethyl-6- (3',4'-dimethylphenylazo)-aminobenzene (I) for many hours with malonic ester in dioxane in the presence of small amounts of acetic acid or heating at 170-180°C for 10-20 minutes with some drops of concentrated hydrochloric acid led to the formation of a yellow crystalline substance (IV) with composition  $C_{21}H_{25}O_3N_3$ ;  $\lambda_{\max}$  243, 350 m $\mu$ . This substance was not a substituted quinoxaline, since it gave a sharp melting point depression when mixed with 6, 7-dimethyl-2-hydroxyquinoxaline-3-carboxylic acid of known structure prepared from alkaline hydrolysis of the Schiff base from 3, 4-dimethyl-o-phenylenediamine and alloxan. The ultraviolet absorption spectrum of substance (IV) differed from the spectrum of 6,7-dimethyl-2-hydroxyquinoxaline-3-carboxylic acid. If the condensation of the azo dye (I) with malonic ester was carried out in glacial acetic acid, we obtained compound (V) with empirical formula  $C_{35}H_{39}O_2N_6$ ,  $\lambda_{\max}$  255 and 344 m $\mu$ .

Acetylation of the azo dye (I) with acetic anhydride at 30-50°C led to formation of the corresponding 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-acetanilide (VI) with absorption bands 242 and 345 m $\mu$  in the ultraviolet spectrum, which agreed well enough with the absorption maxima of compounds (IV) and (V) (see Fig. 2).

Acylation of the primary amino group of azo dye (I) led to a characteristic change of its ultraviolet spectrum. In all three substances (IV, V, and VI) there was no maximum at 436 m $\mu$  [12], which is characteristic for the chromophore system of azo dye (I). There was also a bathochromic shift of the second maximum by 13-17 m $\mu$ , and also a marked lowering of its intensity. For compounds (IV) and (V) obtained by condensation of the azo dye with malonic ester there was also a characteristic absorption maximum in the shorter wavelength portion (240-260 m $\mu$ ), apparently related to the presence of the conjugated carbonyl group.

The structure of the substances (IV and V) was shown by us on the basis of their properties, elementary composition and also the similarity of their ultraviolet spectra with the spectrum of acetylated azo dye (VI); condensation of 3, 4-dimethyl-6-(3,4'-dimethylphenylazo)-aminobenzene (I) with malonic ester leads to acylation of the amino group of the azo dye; in dioxane there is formed the monoamide (IV); in acetic acid, the diamide (V). In this reaction there is no splitting of the -N=N- group.



Comparison of the infrared spectra of the starting azo dye and its three derivatives finally confirmed the structure of compounds (V) and (VI) (See Fig. 3) \*.

\* The study of the infrared spectra was carried out on an IKS-11 spectrograph by L. V. Luk'yanova for which we express thanks.

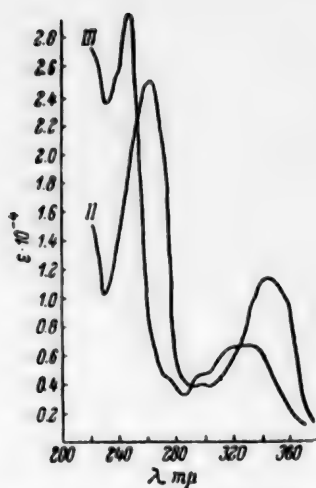


Fig. 1. Ultraviolet spectra of quinoxalines (in alcohol). 2-Phenyl-6, 7-dimethylquinoxaline (II); 2, 6, 7-trimethyl-3-carbomethoxyquinoxaline (III).

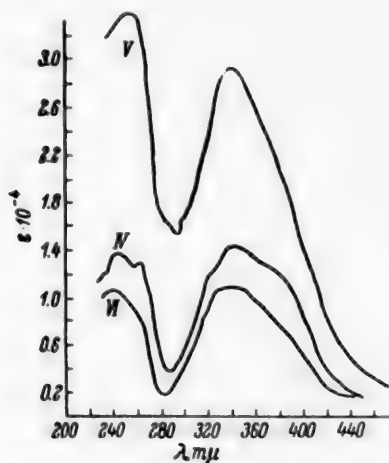


Fig. 2. Ultraviolet spectra of acylated derivatives of azo dyes (in alcohol). 3,4-Dimethyl-6-(3',4'-dimethylphenylazo)-acetanilide (VI); 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-carbomethoxyacetanilide (IV); malonylbis-[3,4-dimethyl-6-(3',4'-dimethylphenylazo)-anilide] (V).

band at  $1735\text{ cm}^{-1}$  which is characteristic for carbonyl in ester groups. A rather intense band at  $1460\text{ cm}^{-1}$  is found in all cases from the deformation asymmetric oscillation of the methyl groups; symmetrical deformation oscillation of these groups causes the appearance of a band at  $1380\text{ cm}^{-1}$ , while absorption bands at  $2800\text{--}3000\text{ cm}^{-1}$  are characteristic for valence oscillation of the bond C-H.

Besides malonic ester, we condensed malonic acid, its diamide, and dinitrile with ortho-aminoazo compounds; but after many hours of boiling we isolated only the starting substances. While condensation of barbituric acid with

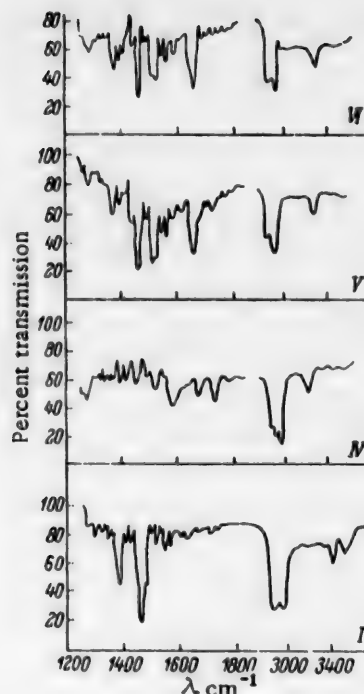
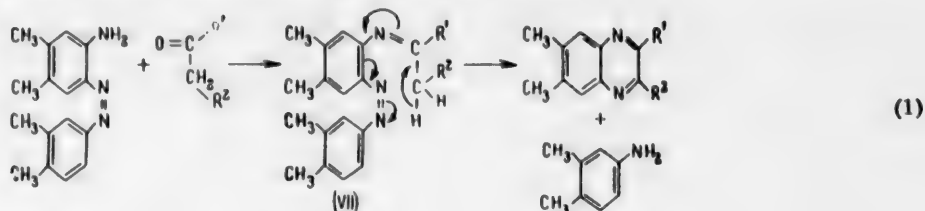


Fig. 3. Infrared spectra of 3,4-dimethyl-6-(3', 4'-dimethylphenylazo)-aminobenzene and its derivatives. 3,4-Dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (I); 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-carbomethoxyacetanilide (IV); malonylbis-[3,4-dimethyl-6-(3',4'-dimethylphenylazo)-anilide] (V); 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-acetanilide (VI).

The spectrum of azo dye (I) had two bands of valence oscillation N-H at  $3411$  and  $3530\text{ cm}^{-1}$  depending on symmetrical and asymmetrical oscillation of the hydrogen atoms which is characteristic for the amino group. These bands are not found in the acylated derivatives (IV-VI). In distinction from the azo dye (I), in the acetyl derivative (VI) there is a band with a frequency of  $3270\text{ cm}^{-1}$  (secondary amine); also there is the so-called band of amide-I at  $1658\text{ cm}^{-1}$ , corresponding to symmetrical oscillation of the amide carbonyl group. The same absorption band is present in the infrared spectrum of the monoamide (IV) and diamide (V), and the frequency of valence oscillation of N-H in these compounds is respectively  $3260$  and  $3270\text{ cm}^{-1}$ , and the bands for amide-I,  $1670$  and  $1658\text{ cm}^{-1}$ . In the spectrum of the monoamide (IV) there is a

azo dyes (I) gives lumichrome, its reaction with malonic ester does not lead to the corresponding quinoxaline, and the reaction remains at the stage of formation of amide. The monoamide (IV) even as a result of long heating in butyl acetate with acetic acid is not converted into 6, 7-dimethyl-2-hydroxyquinoxaline-3-carboxylic acid.

Evidently there is first obtained the intermediate Schiff base (VII) which is a necessary condition for the formation of a pyrazine ring; compound (VII) then undergoes intramolecular cyclization accompanied by splitting of the azo group which is connected with a specific rearrangement of the electron density.



#### EXPERIMENTAL

**6,7-Dimethyl-2-phenylquinoxaline (II).** In a flask with an air condenser we placed 5 g (0.021 mole) of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (I) [12] and 10 g (0.083 mole) of acetophenone; we added three drops of concentrated hydrochloric acid and heated for 15 minutes at 180-190°C. After cooling, the dark brown melt solidified. We added to the flask 5 ml of 4% sodium hydroxide solution and distilled the xylidine which formed and the excess acetophenone with steam. The residue after cooling was separated and recrystallized, first from alcohol with charcoal, and then from toluene. We obtained 3.43 g (70%) of 6,7-dimethyl-2-phenylquinoxaline (II) in the form of yellow brown prisms with m.p. 128-129°C. The absorption spectrum (in alcohol) showed  $\lambda_{\max}$  263 m $\mu$  ( $\epsilon$   $2.49 \cdot 10^4$ ) and 346 m $\mu$  ( $\epsilon$   $1.13 \cdot 10^4$ ). The substance dissolved well in ether, aromatic hydrocarbons, and was little soluble in cyclohexane.

Found %: C 82.25, 82.10; H 6.04, 6.08; N 11.93, 12.19.  $C_{16}H_{14}N_2$ . Calculated %: C 82.01; H 6.03; N 11.96.

Under analogous conditions by heating 1 g of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (I) and 5 g of acetophenone with 2 ml of glacial acetic acid for 20 minutes at 180-190°C we obtained 0.24 g (25%) of 6,7-dimethyl-2-phenylquinoxaline (II).

**2,6,7-Trimethyl-3-carbethoxyquinoxaline (III)** was obtained by a method analogous to that given above from 5 g (0.021 mole) of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (I) and 3 g (0.023 mole) of acetoacetic ester. After recrystallization from a mixture of alcohol and cyclohexane (1:1) we isolated 3.1 g (60.8%) of 2,6,7-trimethyl-3-carbethoxyquinoxaline (III) in the form of cream colored needles with m.p. 90°C. Absorption spectrum (in alcohol):  $\lambda_{\max}$  248 m $\mu$  ( $\epsilon$   $2.95 \cdot 10^4$ ) and 328 m $\mu$  ( $\epsilon$   $0.675 \cdot 10^4$ ).

Found %: C 68.75, 68.54; H 6.60, 6.79; N 11.42, 11.12.  $C_{14}H_{16}O_2N_2$ . Calculated %: C 68.78; H 6.60; N 11.46.

Under analogous conditions by heating 1 g of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (I) and 3 g of acetoacetic ester with 0.5 g of succinic acid we obtained 0.34 g (33.5%) of 2,6,7-trimethyl-3-carbethoxyquinoxaline (III).

**3,4-Dimethyl-6-(3',4'-dimethylphenylazo)-carbethoxyacetanilide (IV).** a) **Condensation in dioxane.** In a flask with a reflux condenser we placed 2.5 g of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (I), 3 ml of malonic ester, 30 ml of dioxane, and 0.5 ml of glacial acetic acid; the mixture was boiled for 42 hours. After cooling, the solvent was distilled off in a vacuum, the residue was separated from the mother liquor and washed on the filter with cyclohexane. After recrystallization from a mixture of alcohol-dioxane (10:1) we obtained 1.33 g (36.4%) of 3,4-dimethyl-6-(3',4'-dimethylphenylazo)-carbethoxyacetanilide (IV); orange crystals with m.p. 163-164°C. Absorption spectrum (in alcohol):  $\lambda_{\max}$  242 m $\mu$  ( $\epsilon$   $1.38 \cdot 10^4$ ), 262 m $\mu$  ( $\epsilon$   $1.24 \cdot 10^4$ ), and 350 m $\mu$  ( $\epsilon$   $1.30 \cdot 10^4$ ). The substance dissolved well in dioxane and acetic acid, soluble in alcohol, poorly soluble in aqueous acids and alkalis.

Found %: C 68.88, 69.10; H 7.23, 7.13; N 11.32, 11.19.  $C_{21}H_{25}O_3N_3$ . Calculated %: C 68.70; H 6.86; N 11.44.

b) Condensation in Excess Malonic Ester. We heated a mixture of 5 g of 3,4-dimethyl-(3',4'-dimethylphenylazo)-aminobenzene (I) and 10 g of malonic ester with several drops of concentrated hydrochloric acid at 170-180°C for 20 minutes. After cooling the reaction mixture, the substance was separated and recrystallized as described above. We obtained 3.95 g (52.7%) of 3, 4-dimethyl-6-(3',4'-dimethylphenylazo)-carbethoxyacetanilide (IV) with m.p. 163-164°C.

Malonyl-bis-[3,4-dimethyl-6-(3',4'-dimethylphenylazo)-anilide] (V). We boiled 2.15 g of 3, 4-dimethyl-(3',4'-dimethylphenylazo)-aminobenzene (I) and 3 ml of malonic ester in 30 ml of glacial acetic acid for 48 hours and after analogous treatment obtained 1.25 g (22%) of malonyl-bis-[3,4-dimethyl-6-(3',4'-dimethylphenylazo)-anilide] (V): yellow plates with m.p. 145-146°C (from alcohol). Absorption spectrum (in alcohol):  $\lambda_{\max}$  255 m $\mu$  ( $\epsilon$   $3.4 \cdot 10^4$ ) and 344 m $\mu$  ( $\epsilon$   $2.94 \cdot 10^4$ ).

Found %: C 72.76, 72.68; H 6.74, 6.90; N 14.43, 14.47.  $C_{36}H_{38}O_3N_6$ . Calculated %: C 73.13; H 6.66 N 14.63.

3, 4-Dimethyl-6-(3',4'-dimethylphenylazo)-acetanilide (VI). To 1 g of 3, 4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene (I) was added 5 ml of acetic anhydride and the mixture was heated under reflux for one hour at 35-45°C; after 10 minutes from the start of the reaction the brown melt solidified. The solid product was pressed free of the liquid and washed with cyclohexane on the filter; we obtained 1.15 g of 3, 4-dimethyl-6-(3',4'-dimethylphenylazo)-acetanilide (VI) in the form of yellow prisms with m.p. 162-163°C (from alcohol); the yield was almost quantitative. Absorption spectrum:  $\lambda_{\max}$  242 m $\mu$  ( $\epsilon$   $1.07 \cdot 10^4$ ) and 345 m $\mu$  ( $\epsilon$   $1.12 \cdot 10^4$ ).

Found %: C 73.15, 73.15; H 7.06, 7.12; N 14.08, 14.29.  $C_{18}H_{21}ON_3$ . Calculated %: C 73.40; H 7.16; N 14.22.

#### SUMMARY

The reaction of condensation of 3, 4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene with substances which contain a carbonyl group and a mobile  $\alpha$ -hydrogen atom, for example, acetoneacetic ester and acetophenone, leads to substituted quinoxalines, while the reaction of this azo dye with malonic ester occurs like the usual reaction of amide formation.

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# THE PREPARATION OF TRANS-ISOLIMONENE

I. S. Kozhina and A. S. Danilova

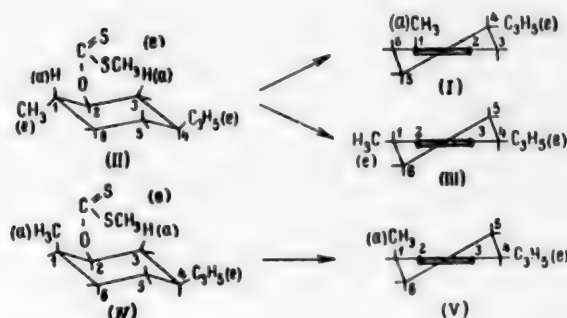
Botanical Institute, Academy of Sciences USSR, and Leningrad State University

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In the thermal decomposition of the methyl ester of dihydrocarvylxanthogenic acid L. A. Chugaev [1] obtained along with limonene (I) a new hydrocarbon, isolimonene. Later G. V. Pigulevskii and I. S. Kozhina [2] repeated this reaction in order to obtain a preparation of isolimonene free from admixtures of limonene and to explain the structure of isolimonene. They showed that isolimonene is  $\Delta^2,8(9)$ -p-menthadiene. However, the isolimonene which was obtained was not stereochemically homogeneous, since G. V. Pigulevskii and I. S. Kozhina started from a mixture of dihydrocarveol and isodihydrocarveol which was obtained in the reduction of carvone with sodium and alcohol. Since the decomposition of xanthogenic esters occurs as a reaction of cis-splitting, there is formed from the methyl ester of dihydrocarvylxanthogenic acid (II) trans-isolimonene, and from the methyl ester of isodihydrocarvylxanthogenic acid (IV), the cis-isolimonene. Therefore the isolimonene which was obtained should be a mixture of both forms (III) and (V).



Our problem was to obtain a homogeneous trans-isolimonene, free from admixtures of cis-limonene. For this purpose it was most of all necessary to prepare for the starting product a stereochemically homogeneous dihydrocarveol. For this we used the method of Johnston and Read [3], somewhat modified by us, and we obtained a crystalline 3, 5-dinitrobenzoate of dihydrocarveol with m.p. 121°C. (We prepared the starting dihydrocarveol according to Wallach [4]). After saponification of the 3, 5-dinitrobenzoate we isolated dihydrocarveol whose physical constants agreed with the constants of the dihydrocarveol obtained by L. A. Chugaev [1] in the saponification of crystalline dihydrocarvylxanthogenamide, and also with the constants of the preparation of dihydrocarveol isolated by Schmidt [5] from the etherial oil of caraway.

The combination scattering spectra which we obtained for the stereochemically homogeneous dihydrocarveol basically agreed with the spectrum which we obtained for the starting mixture of dihydrocarveols (see also [6]). In the dihydrocarveol spectrum there is a very intense line  $\Delta \nu$  770  $\text{cm}^{-1}$  which is characteristic for alcohols with equatorial hydroxyls. The line  $\Delta \nu$  750  $\text{cm}^{-1}$  is characteristic for neodihydrocarveol [7], in the molecule of which there is a hydroxyl group in the axial position, and this line is completely absent in the spectra of all the dihydrocarveol preparations which we obtained.

We also obtained the infrared spectrum of stereochemically homogeneous dihydrocarveol\* (Fig. 1). The presence in this spectrum of the absorption band 1048  $\text{cm}^{-1}$  is apparently connected with the presence of an equatorial

\* In the rest of the paper we will call the stereochemically homogeneous dihydrocarveol merely dihydrocarveol.

hydroxyl group in the molecule of dihydrocarveol, as occurs in a number of secondary steroid alcohols. It is true that according to the data of Chiurdoglu [8] in the spectra of secondary alcohols of the cyclohexane series there is no definite frequency in this region for the C-O which corresponds to an equatorial arrangement of the hydroxyl. Unfortunately, we did not have at our disposal any neodihydrocarveol, and so we could not compare its spectrum with the spectrum of dihydrocarveol in order to answer this question.

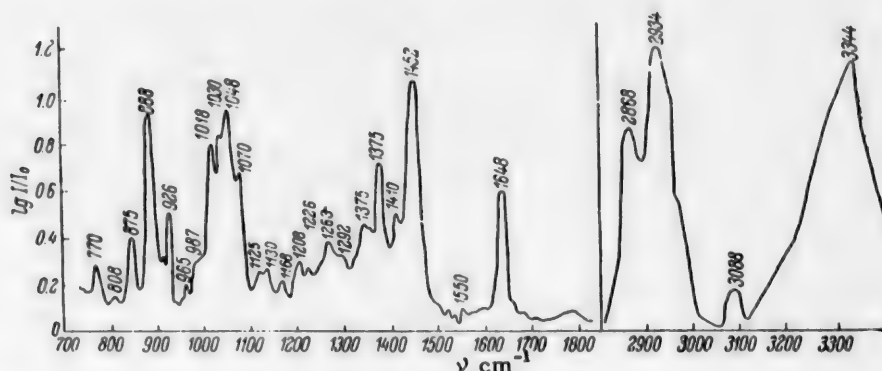
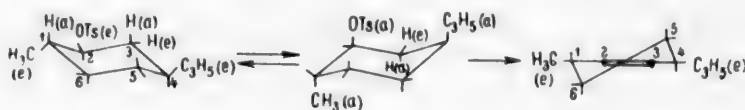


Fig. 1. Infrared absorption spectrum of dihydrocarveol.

We should mention that in the reaction of dihydrocarveol, obtained according to Wallach [4], with 3, 5-dinitrobenzoyl chloride we found along with the crystalline dihydrocarveol 3, 5-dinitrobenzoate also a liquid product. It was probably a mixture of unreacted starting alcohol, dihydrocarveol 3, 5-dinitrobenzoate, and also isodihydrocarveol 3, 5-dinitrobenzoate which is a liquid, according to Schmidt [5]. However, we were not able to show the presence of isodihydrocarveol derivatives in this mixture.

In obtaining the stereochemically homogeneous dihydrocarveol we did not use the xanthogenate method of L. A. Chugaev for dehydration of dihydrocarveol, since on this there would be formed a mixture of *trans*-isolimonene and limonene. We used the method of Huckel and co-workers [9] which consists in decomposition of the *p*-toluenesulfonic esters of alcohols by the action of sodium alcoholate.

Starting from the mechanism of this reaction as a reaction of *trans*-splitting, we could expect the formation only of the *trans*-isomer of isolimonene in the case of dehydration of dihydrocarveol.



By the action of *p*-toluenesulfonyl chloride on dihydrocarveol under the conditions proposed by Phillips [10] for preparing the *p*-toluenesulfonate of menthol, we obtained the *p*-toluenesulfonate of dihydrocarveol (yield 90 %), which melted at 65°C.

In the reaction of *p*-toluenesulfonyl chloride with a mixture of dihydrocarveols obtained directly by reduction of carvone we also obtained a crystalline product with m.p. 65°C, it is true with a yield of 64%. A sample of this mixed with the *p*-toluenesulfonate of dihydrocarveol gave no melting point depression. Therefore, there was no further need for the troublesome preliminary purification of the dihydrocarveol through the 3, 5-dinitrobenzoate.

The reaction of dihydrocarveol *p*-toluenesulfonate with sodium ethylate was carried out under the conditions worked out by Huckel and co-workers [9] for menthol - toluenesulfonate. After the usual treatment, the reaction products were distilled in a rectifying column (16 theoretical plates). As a result we obtained three products (see Table).



Products of Reaction of Dihydrocarveol p-Toluenesulfonate with Sodium Ethylate

Name of compound	B. p.(pressure in mm)	$d_4^{20}$	$n_D^{20}$	$[\alpha]_D^{20}$	Yield, %
Trans-isolimonene	65° (25)	0.8360	1.465	-184.2°	28.5
Ethyl ether of neodihydrocarveol	95 (25)	0.8679	1.453	- 50.0	21.6
Dihydrocarveol	98 (9)	0.9210	1.478	+ 35.0	30.0

The first product (hydrocarbon) had physical constants very close to the constants of isolimonene [2]. However, it had a considerably higher value for the specific rotation ( $[\alpha]_D^{20}$  - 184.2°C) compared to the value found by G. V. Pigulevskii and I. S. Kozhina ( $[\alpha]_D^{20}$  - 148.9°C). This can be explained by the fact that in our preparation of trans-limonene admixtures of cis-limonene were absent.

This isolimonene did not give a crystalline tetrabromide, which is characteristic for this hydrocarbon [1].

The combination scattering spectrum of this hydrocarbon agreed with the previously published spectrum of isolimonene [2] \*. For further characterization of trans-isolimonene we also took its infrared spectrum (Fig. 2).

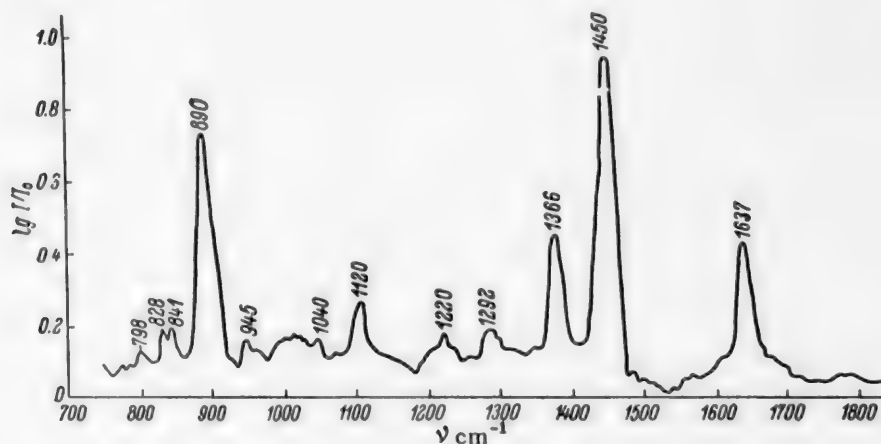


Fig. 2. Infrared absorption spectrum of trans-isolimonene.

The second product of decomposition of dihydrocarveol p-toluenesulfonate to judge by the results of elementary analysis and determination of ethoxyl groups, is an ethyl ether with the composition  $C_{10}H_{17}OC_2H_5$ .

Huckel and co-workers [11] showed that the formation of ethyl ethers by the action of sodium ethylate on p-toluenesulfonates of secondary alcohols occurs with a Walden inversion. To decide whether our product is the ether of neodihydrocarveol or the ether of dihydrocarveol, we decided to synthesize the ethyl ether of dihydrocarveol from potassium dihydrocarveolate and ethyl iodide under conditions which exclude the Walden inversion. It was shown that ether has the same sign of rotation as the starting alcohol, while the ethyl obtained in the reaction of dihydrocarveol p-toluenesulfonate with sodium ethylate has the opposite sign of rotation. Hence, also in the case of dihydrocarveol in the formation of an ether under the conditions of the Huckel reaction there is inversion of configuration at the asymmetric carbon atom, and therefore the ether formed is the ethyl ether of neodihydrocarveol.

\* In the combination scattering spectrum of trans-isolimonene in the usual photographic method for recording the spectrum we do not observe the frequency  $1670\text{ cm}^{-1}$ , characteristic for a secondary-tertiary double bond in the limonene ring. However, on photoelectric recording of the spectrum along with an intense maximum corresponding to a frequency of  $1644\text{ cm}^{-1}$  (characteristic for a secondary-secondary double bond in the isolimonene ring) we find a very small maximum in the region of  $1670\text{ cm}^{-1}$ . Hence we can conclude that in our preparation of trans-isolimonene the possibility is not excluded of the presence of a very small admixture of limonene.

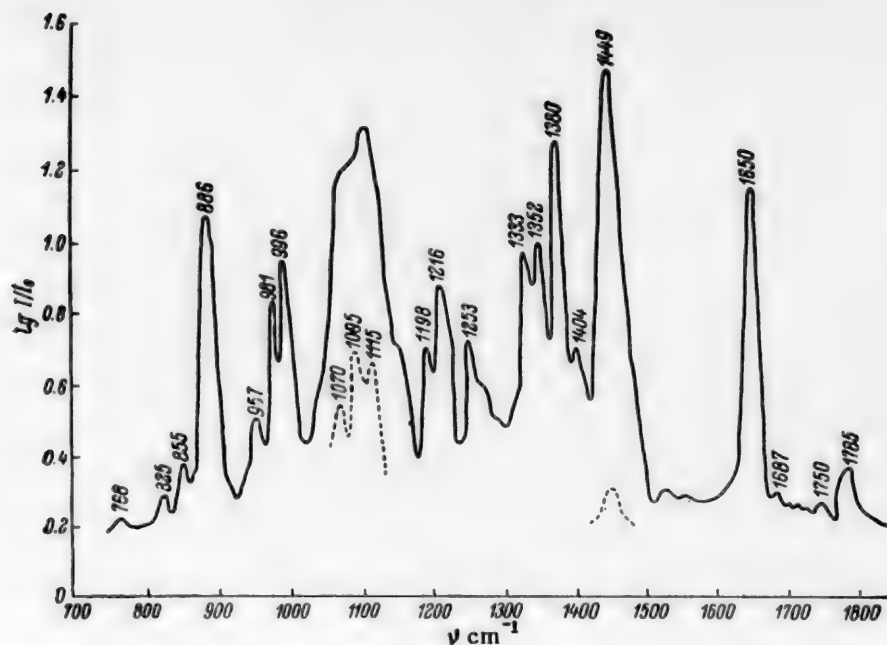


Fig. 3. Infrared absorption spectrum of the ethyl ether of neodihydrocarveol

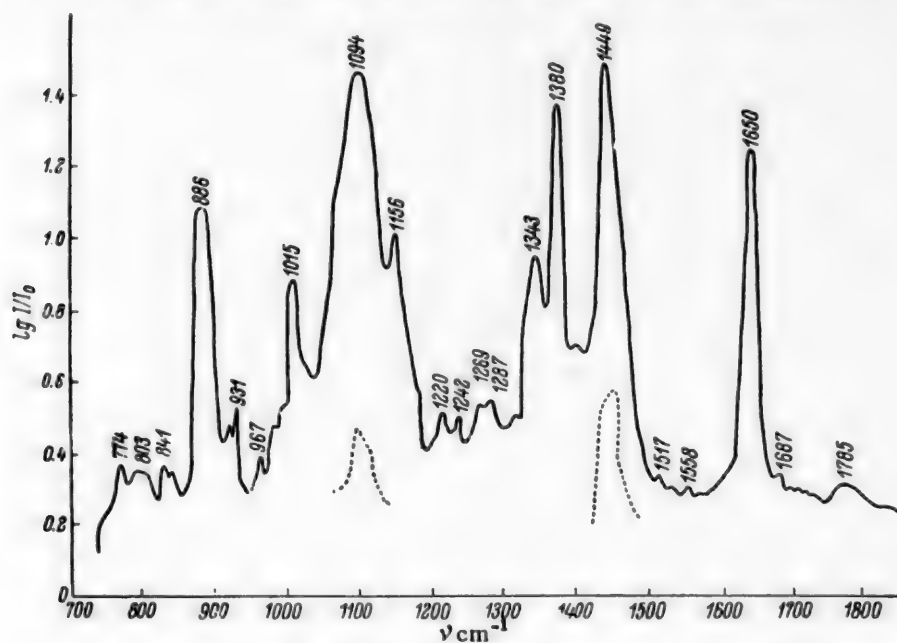


Fig. 4. Infrared absorption spectrum of the ethyl ether of dihydrocarveol.

We have suggested that in the combination scattering spectrum of the ethyl ether of dihydrocarveol and neodihydrocarveol there is a difference connected with the different distribution in space of the ethoxyl groups in the molecules of these compounds. It is known that dihydrocarveol, and neodihydrocarveol have different frequencies of pulsation oscillation of the ring (770 and 750  $\text{cm}^{-1}$ , respectively [12]). However, it has been shown that in the case of the ethyl ethers of these stereoisomeric alcohols the difference in frequency of pulsation oscillation of the rings is not 20  $\text{cm}^{-1}$  as it is in the spectra of the alcohols, but is only 5  $\text{cm}^{-1}$  in all. Thus, in the spectrum of the ethyl ether of dihydrocarveol there is a frequency of 773  $\text{cm}^{-1}$ , while in the spectrum of the ethyl ether of neodihydrocarveol the frequency is 768  $\text{cm}^{-1}$ . Exactly the same frequencies are also found in the infrared spectra of these ethers (see Figs. 3 and 4).

The third product of the reaction of dihydrocarveol p-toluenesulfonate with sodium ethylate, to judge by its physical constants (see table) and combination scattering spectrum, is dihydrocarveol. Confirmation of this comes from the preparation from it of a crystalline p-toluenesulfonate with m.p. 65°C, which in a mixed sample with dihydrocarveol p-toluenesulfonate gives no melting point depression.

Thus, by the action of sodium ethylate on dihydrocarveol p-toluenesulfonate we have succeeded in preparing a stereochemically homogeneous trans-isolimonene (yield 28.5%). A study of this reaction showed that besides the trans-limonene there was also formed the ethyl ether of neodihydrocarveol (yield 21.6%) and dihydrocarveol (yield 30%).

#### EXPERIMENTAL

Reduction of carvone. By the reduction of carvone with sodium and alcohol according to Wallach [4] we obtained a mixture of dihydrocarveols with b.p. 105-109°C (13 mm),  $d_4^{20}$  0.9271,  $n_D^{20}$  1.4790,  $[\alpha]_D^{20} + 29.3^\circ\text{C}$ .

Combination scattering spectrum.  $\Delta\nu$  ( $\text{cm}^{-1}$ ): 293 (3), 320 (1), 351 (1), 389 (1), 444 (1), 460 (1), 474 (1), 499 (2), 509 (1), 554 (1), 581 (1), 770 (5), 830 (1), 886 (2), 927 (1), 956 (1), 982 (1), 990 (1), 1016 (1), 1052 (1), 1110 (1), 1143 (1), 1166 (2), 1252 (1), 1264 (1), 1367 (1), 1434 (5), 1457 (5), 1644 (10).

Preparation of 3, 5-dinitrobenzoate of dihydrocarveol [3]. To a solution of 100 g of a mixture of dihydrocarveol in 300 ml of dry pyridine we added 150 g of 3, 5-dinitrobenzoyl chloride. The reaction mixture was heated to solution of all the chloride, after which it stood for 12 hours at room temperature, and then was poured into cold water. The oily crystals which precipitated were washed first with water to disappearance of odor of pyridine, then with 5% soda solution, and finally with a small amount of cold methylalcohol. Washing with methyl alcohol almost completely freed the crystalline product from admixtures. The yield of crystalline product was 64%. After two recrystallizations from a mixture of ethyl alcohol with ethyl acetate (3:1), m.p. 120-121°C, which agreed with the literature value for dihydrocarveol 3, 5-dinitrobenzoate [3,5].

Saponification of dihydrocarveol 3, 5-dinitrobenzoate. Stereochemical homogeneity of dihydrocarveol. One hundred g of dihydrocarveol 3, 5-dinitrobenzoate (m.p. 120-121°C) was heated for 20 minutes under reflux with a solution of 20 g of KOH in 575 ml of methyl alcohol. The potassium salt of 3, 5-dinitrobenzoic acid which precipitated was filtered off and the filtrate was steam distilled. After salting out with sodium chloride, extracting with ether, drying the ether solution with potash, distillation of the ether, and fractionation in a vacuum, we obtained dihydrocarveol with b.p. 89-90°C (at 5 mm),  $d_4^{20}$  0.9210,  $n_D^{20}$  1.477,  $[\alpha]_D^{20} + 34.5^\circ\text{C}$ .

Combination scattering spectrum.  $\Delta\nu$  ( $\text{cm}^{-1}$ ): 292 (2), 307 (2), 445 (1), 467 (1), 511 (2), 560 (1), 771 (5), 833 (1), 900 (1), 923 (1), 965 (1), 991 (1), 1005 (1), 1059 (1), 1117 (1), 1145 (1), 1166 (1), 1252 (1), 1367 (1), 1435 (5), 1459 (5), 1644 (10).

Preparation of dihydrocarveol p-toluenesulfonate To a cooled solution of 20 g of dihydrocarveol in 20 g of dihydrocarveol in 20 ml of dry pyridine (first dried with KOH and then with BaO) we added 24 g of finely ground p-toluenesulfonyl chloride. The mixture was shaken until the chloride dissolved, then left overnight at room temperature. The crystallized mass was treated with water, then the crystals were separated, washed with water until the odor of pyridine disappeared, and dried in a vacuum. Yield of crude product 90%. After recrystallization from petroleum ether and then alcohol, we obtained 30 g (75%) of pure dihydrocarveol p-toluenesulfonate with m.p. 65°C.

Found %: C 66.38; H 7.77.  $\text{C}_{17}\text{H}_{24}\text{O}_3\text{S}$ . Calculated %: C 66.23; H 7.79.

Analogous experiments were carried out with stereochemically nonhomogeneous dihydrocarveol obtained directly by reduction of carvone. Here also we obtained a crystalline product with m.p. 65°C. Yield 64%. A sample mixed with dihydrocarveol p-toluenesulfonate obtained from stereochemically homogeneous dihydrocarveol gave no melting point depression. However, in this case, along with the crystalline product there was liquid product which we did not study.

Reaction of dihydrocarveol p-toluenesulfonate with sodium ethylate. To a solution of sodium ethylate prepared from 27 g of sodium and 312 ml of anhydrous ethyl alcohol we added 90 g of dihydrocarveol p-toluenesulfonate. The mixture was heated under reflux on a water bath for seven hours and then was left over night at room temperature. The reaction product was steam distilled. After salting out with sodium chloride, extraction with ether, drying with potash, and distilling off the ether we obtained 40 g of a mixture of reaction products. This mixture was fractionated, first in a vacuum in a stream of  $\text{CO}_2$  from a flask with a rectifying column, and then from a column

with 16 theoretical plates, as a result of which we isolated three substances (see Table).

#### Isolimonene.

Combination scattering spectrum  $\Delta \nu$  ( $\text{cm}^{-1}$ ): 329 (2), 450 (1), 471 (1), 506 (1), 590 (5), 710 (1), 729 (1), 770 (6), 830 (1), 887 (3), 947 (2), 968 (3), 1002 (1), 1078 (3), 1113 (4), 1222 (6), 1290 (2), 1315 (1), 1371 (2), 1392 (5), 1430 (8), 1454 (8), 1644 (10).

#### Ethyl Ether of Neodihydrocarveol

Found %: C 79.00; H 12.15;  $\text{C}_2\text{H}_5\text{O}$  24.60.  $\text{C}_{12}\text{H}_{22}\text{O}$ . Calculated %: C 79.12; H 12.09;  $\text{C}_2\text{H}_5\text{O}$  24.72.

Combination scattering spectrum.  $\Delta \nu$  ( $\text{cm}^{-1}$ ): 222 (1), 241 (1), 292 (1), 322 (2), 348 (1), 465 (2), 503 (1), 545 (1), 574 (2), 636 (1), 655 (1), 702 (2), 767 (5), 799 (2), 845 (2), 890 (3), 918 (1), 948 (2), 988 (2), 1033 (2), 1046 (2), 1096 (2), 1113 (2), 1143 (2), 1253 (2), 1275 (1), 1319 (1), 1334 (2), 1437 (4), 1455 (4), 1644 (10).

Dihydrocarveol. Characterized as the p-toluenesulfonate with m.p. 65°C which in a mixed sample with the dihydrocarveol p-toluenesulfonate described above gave no melting point depression.

Combination scattering spectrum.  $\Delta \nu$  ( $\text{cm}^{-1}$ ): 237 (1), 287 (1), 308 (3), 335 (3), 463 (1), 501 (4), 558 (2), 582 (1), 700 (1), 773 (6), 845 (2), 888 (3), 930 (1), 1001 (2), 1018 (2), 1070 (2), 1128 (2), 1142 (1), 1168 (2), 1208 (1), 1253 (1), 1300 (1), 1372 (1), 1437 (4), 1454 (4), 1642 (10).

Preparation of the Ethyl Ether of Dihydrocarveol. In a boiling solution of 25 g of dihydrocarveol in 150 ml of dry xylene we gradually introduced 6.3 g of potassium. After seven hour heating on an oil bath all the potassium dissolved. To the resulting solution of potassium dihydrocarveolate we added 60 g of ethyl iodide and heated the mixture for 12 hours at 100-120°C. The precipitate of potassium iodide was filtered off and the unreacted ethyl iodide and xylene were distilled from the filtrate in a small vacuum. We added to the residue to bind unreacted dihydrocarveol a little potassium, and the mixture was heated on an oil bath for two hours, after which it was distilled in a vacuum. We obtained 6 g of ethyl ether of dihydrocarveol with b.p. 75°C (3 mm),  $n_D^{20}$  1.454 and  $a_D^{20} + 52^\circ\text{C}$ .

Solid potassium dihydrocarveolate remained in the distillation flask, to which, after its solution in xylene and removal of unreacted potassium we again added ethyl iodide. Then the above operation was repeated. After distillation over potassium we obtained 6 g more of ether. Both portions were combined and distilled in a column. We obtained the ethyl ether of dihydrocarveol with b.p. 99°C (12 mm),  $n_D^{20}$  1.453,  $d_4^{20}$  0.8680 and  $[a]_D^{20} + 66.0^\circ\text{C}$ .

Found %: C 78.98; H 12.07;  $\text{C}_2\text{H}_5\text{O}$  24.75.  $\text{C}_{12}\text{H}_{22}\text{O}$ . Calculated %: C 79.12; H 12.09;  $\text{C}_2\text{H}_5\text{O}$  24.72.

#### SUMMARY

1. For the first time we have obtained stereochemically homogeneous transisolimonene (trans- $\Delta^{2,8(9)}$ -p-menthadiene).
2. We have obtained the p-toluenesulfonic acid ester of dihydrocarveol and have studied its reaction with sodium ethylate.
3. We have obtained and characterized the ethyl ethers of dihydrocarveol and neodihydrocarveol.
4. We have taken the combination light scattering spectra and infrared spectra of trans-isolimonene, dihydrocarveol, the ethyl ether of dihydrocarveol, and the ethyl ether of neodihydrocarveol.

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**p-DI-(2)CHLOROETHYL)-AMINO-dl - PHENYLALANINE ("SARCOLYSIN")  
AND ITS DERIVATIVES.**

**VII. HALOGEN SUBSTITUTION IN THE RING OF SARCOLYSIN DERIVATIVES**

E. N. Shkodinskaya, E. M. Kurdyukova, and A. Ya. Berlin

Institute of Experimental and Clinical Oncology, Academy of Medical Sciences, USSR

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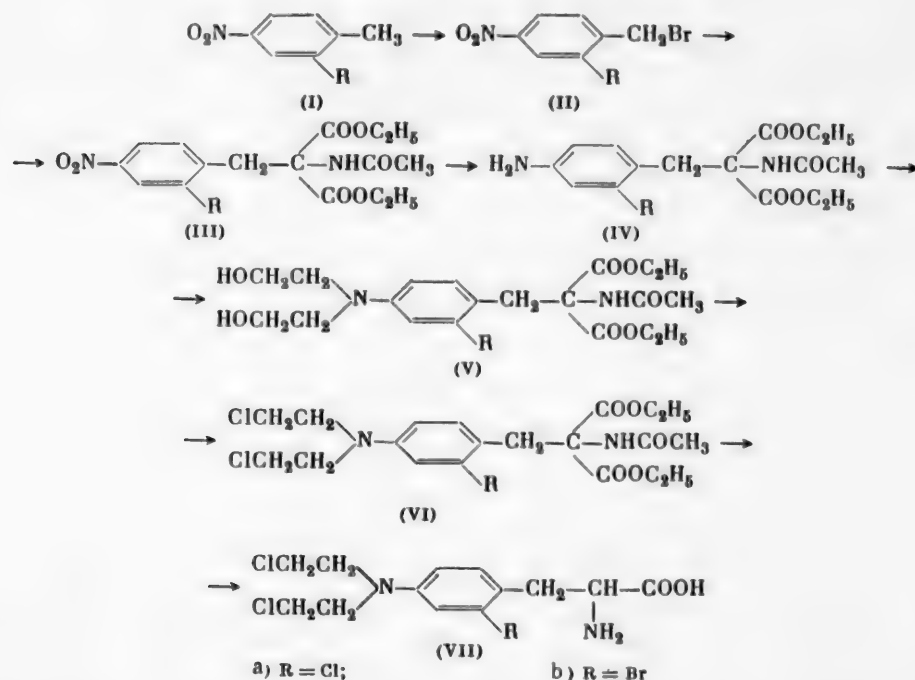
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Up to the present time many different derivatives of sarcolysin both on the carboxyl and the amino groups [1-3] and various sarcolysin isomers [4,5] have been synthesized. Since all these compounds differ from each other not only in their chemical and physicochemical properties, but also in the nature of their action on tumors, it seemed interesting to us to continue to seek anticancer preparations in the sarcolysin series in order to change the relative toxicity and also the specific direction of action against definite types of malignant neoplasms.

We decided to introduce changes in the sarcolysin molecule by putting a halogen atom in the aromatic ring. It is worth mentioning that one of the possible preparations of this type ("fluoro-metasarcolysin") has already been studied in an experiment on animals [6] and has shown itself a rather interesting substance.

In the present work we describe the synthesis of o-chloro- and o-bromo-p-di-(2-chloroethyl)-amino-dl-phenylalanine, which was carried out on the basis of the scheme analogous to that for sarcolysin [7] and its meta-isomer [4].



The starting substance in the synthesis of o-chlorosarcolysin (VIIa) was o-amino-p-nitrotoluene from which we obtained o-chloro-p-nitrotoluene (Ia) by diazotization. This was brominated with bromosuccinimide [9] with formation of o-chloro-p-nitrobenzyl bromide (IIa). o-Chloro-p-nitrobenzylacetaminomalonic ester (IIIa) was obtained



by condensation of the starting benzyl bromide (IIa) with acetylaminomalonic ester, and then this was converted by catalytic hydrogenation into *o*-chloro-*p*-aminobenzylacetylaminomalonic ester (IVa). Skeletal nickel was shown not to be the catalyst to use; in its presence the reaction occurs slowly and with poor yield; instead 5% Pd on charcoal was used.

Hydroxyethylation of the above product (IVa) was carried out in dilute acetic acid by the action of excess ethylene oxide, and the resulting *o*-chloro-*p*-di(2-hydroxyethyl)-aminobenzylacetylaminomalonic ester (Va) was converted into *o*-chloro-*p*-di-(2-chloroethyl)-aminobenzylacetylaminomalonic ester (VIa) by the action of thionyl chloride in chloroform. When the *o*-chloro-*p*-di-(2-chloroethyl)-aminobenzylacetylaminomalonic ester (VIa) was boiled with concentrated hydrochloric acid it formed the hydrochloride of *o*-chloro-*p*-di-(2-chloroethyl)-amino-*dl*-phenylalanine (VIIa) ("o-chlorosarcosyn") which easily lost hydrogen chloride (especially in the process of drying) and was converted into the base. From the base (VIIa) we also easily obtained *o*-chlorosarcosyn dihydrochloride.

In an entirely analogous way, starting from the same *o*-amino-*p*-nitrotoluene, through (IB), (IIB), (IIb), (IVb), (Vb), and (VIb) we synthesized *o*-bromosarcosyn (VIb), isolated in the form of a sufficiently stable hydrochloride.

It is interesting to note that substances (VIa) and (VIb), which have the respective melting points 158.5-159.5° and 157.5-158° and differ from each other only in the different halogen atom in the *o*-position do not give melting point depressions in mixed samples.

All the analytical investigations were carried out in the analytical laboratory of our institute under the direction of A. D. Chinaeva.

## EXPERIMENTAL

### 1. Synthesis of *o*-Chlorosarcosyn.

*o*-Chloro-*p*-nitrobenzyl bromide (IIa). A mixture of 10.9 g (0.0635 mole) of *o*-chloro-*p*-nitrotoluene, 11.5 g (0.0645 mole) of bromosuccinimide, 50 mg of benzoyl peroxide and 75 ml of dry CCl<sub>4</sub> was boiled with illumination by a lamp (150 W) for two hours. The succinimide which precipitated was filtered off and the filtrate was evaporated in a vacuum. The residue was left overnight in a refrigerator under petroleum ether, the crystals which separated were filtered off and recrystallized from alcohol. Yield 9.35 g (62.5%), m.p. 46.47°C (according to the literature [10], m.p. 49-50°C).

*o*-Chloro-*p*-nitrobenzylacetylaminomalonic ester (IIIa). In a warm solution of sodium ethylate [50 ml of anhydrous alcohol and 0.86 g (0.0374 mole) of sodium] with energetic stirring we added 8.1 g (0.0373 mole) of acetylaminomalonic ester. After solution of the latter in the reaction mass, we added dropwise with stirring 9.32 g (0.0372 mole) of *o*-chloro-*p*-nitrobenzyl bromide (IIa) in 50 ml of dry benzene. The mixture was stirred for two hours more and left overnight. Then it was evaporated dry, the remaining crystals were washed with water and recrystallized from alcohol. After drying, we obtained 9.3 g (65%) of substance with m.p. 144-145°C. After a second recrystallization from alcohol we isolated long colorless prisms with m.p. 145-146°C.

Found %: C 49.76; H 5.00; N 7.20; Cl 9.01. C<sub>16</sub>H<sub>19</sub>O<sub>7</sub>N<sub>2</sub>Cl. Calculated %: C 49.68; H 4.95; N 7.24; Cl 9.17.

*o*-Chloro-*p*-aminobenzylacetylaminomalonic ester (IVa). A solution of 2.2 g of (IIIa) in 18 ml of 95% alcohol in the presence of 0.2 g of 5% Pd on charcoal was shaken with hydrogen for one hour at 45-50°C. After removal of the catalyst and a large part of the solvent the crystals were filtered off. We obtained 1.7 g (84%) of substance with m.p. 163.5-165°C. Recrystallization from alcohol gave colorless crystals in the form of dense prisms with m.p. 165-166°.

Found %: C 53.83; H 5.89; N 7.83; Cl 9.51. C<sub>16</sub>H<sub>21</sub>O<sub>5</sub>N<sub>2</sub>Cl. Calculated %: C 53.87; H 5.93; N 7.85; Cl 9.94.

*o*-Chloro-*p*-di(2-hydroxyethyl)-aminobenzylacetylaminomalonic ester (Va). To a cooled solution of 1.7 g (0.00478 mole) of (IVa) in 10 ml of 50% acetic acid we added 2 ml (0.0436 mole) of freshly distilled ethylene oxide and left the mixture for a day. The resulting clear solution was poured into 100 ml of cold water and neutralized with KHCO<sub>3</sub> to pH 7. The oil which precipitated was extracted with ethyl acetate and the solution was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>. The residue after evaporation was recrystallized from dry benzene. We obtained 1.9 g (89%) of substance with m.p. 128.5-130°C. An analytically pure sample was obtained by recrystallization from benzene. Colorless crystals in the form of dense prisms with m.p. 129.5-130°C.

Found %: C 57.26; H 6.46; N 5.95. C<sub>20</sub>H<sub>29</sub>O<sub>7</sub>N<sub>2</sub>Cl · 1/2 C<sub>6</sub>H<sub>6</sub>. Calculated %: C 57.07; H 6.67; N 5.79.



After drying in a vacuum (2-3 mm) for 15 hours at 84° (temperature of boiling dichloroethane) we obtained a substance without solvent of crystallization.

Found %: C 53.95; H 6.46; N 6.31; Cl 7.40.  $C_{20}H_{29}O_7N_2Cl$ . Calculated %: C 53.99; H 6.57; N 6.30; Cl 7.97.

p-Chloro-p-di-(2-chloroethyl)-aminobenzylacetylaminomalonic ester (VIa). To a solution of 7.3 g (0.0152 mole) of (Va) in 100 ml of dry chloroform was added 12 ml (0.0612 mole) of thionyl chloride and the mixture was boiled for 15 minutes. After evaporation in a vacuum and later recrystallization of the solid residue from alcohol we obtained 4.88 g of substance (62%) with m.p. 156-158°C. Repeated recrystallizations gave m.p. 158.5-159°C.

Found %: C 49.85; H 5.75; N 5.90; Cl 22.06.  $C_{20}H_{27}O_5N_2Cl_3$ . Calculated %: C 49.86; H 5.65; N 5.82; Cl 22.09.

o-Chloro-p-di-(2-chloroethyl)-amino-dl-phenylalanine ("o-chloro-sarcosyn") (VIIa). A solution of 7.2 g of (VIa) in 80 ml of hydrochloric acid (d 1.17) was boiled for four hours. The residue after evaporation in a vacuum (at a temperature not above 40°C) was a clear thick oil which solidified when ground with water. After filtration and drying we obtained 4.7 g (83.5%) of substance with m.p. 170-172°C (decomposition). Two recrystallizations from 35% alcohol gave a colorless crystalline substance with m.p. 178-180°C (decomposition). The substance was soluble in alcohol, poorly so in water, and insoluble in the usual organic solvents.

Found %: Cl 37.44, 37.59.  $C_{13}H_{17}O_2N_2Cl_3 \cdot HCl$ . Calculated %: Cl 37.69.

The hydrochloride of o-chloro-p-di-(2-chloroethyl)-amino-dl-phenylalanine which we obtained on long drying in a vacuum desiccator lost a molecule of hydrogen chloride and changed to the base (VII) which was poorly soluble in ethanol, somewhat better in methanol, insoluble in water and the other usual organic solvents. Colorless plates with m.p. 166-168°C (decomposition) (from methanol).

Found %: C 45.72; H 5.29; N 8.43; Cl 31.07.  $C_{13}H_{17}O_2N_2Cl_3$ . Calculated %: C 45.95; H 5.03; N 8.25; Cl 31.32.

When base (VII) was treated with concentrated hydrochloric acid and the solution was evaporated in a vacuum to dryness, we obtained a dihydrochloride in the form of colorless crystals with m.p. 179-181°C, easily soluble in alcohol and water.

Found %: C 37.88; H 4.79; Cl 42.26.  $C_{13}H_{17}O_2N_2Cl_3 \cdot 2HCl$ . Calculated %: C 37.83; H 4.64; Cl 42.86.

## 2. Synthesis of o-bromosarcosyn.

o-Bromo-p-nitrobenzyl bromide (IIb). This was obtained like (IIa) by boiling 13.4 g (0.062 mole) of o-bromo-p-nitrotoluene with 11.05 g (0.062 mole) of bromonitrimide and 50 mg of benzoyl peroxide in 70 ml of dry  $CCl_4$  for three hours. After recrystallization from alcohol, the yield was 12 g (65.5%). Two recrystallizations from alcohol gave colorless needles with m.p. 63.64°C.

Found %: Br 53.76.  $C_7H_5O_2NBr$ . Calculated %: Br 54.18.

o-Bromo-p-nitrobenzylacetylaminomalonic ester (IIIb). By condensation of 17.45 g (0.0592 mole) of (IIb) in 70 ml of dry benzene with 12.85 g (0.0593 mole) of acetylaminomalonic ester in a solution of sodium ethylate [1.36 g (0.0593 atm) of metallic sodium in 70 ml of anhydrous alcohol] under conditions analogous to those in preparing (IIIa) we isolated after recrystallization from benzene and anhydrous alcohol 16.3 g (64%) of substance in the form of colorless needles with m.p. 143-144°C.

Found %: C 44.58; H 4.49; N 6.39; Br 18.76.  $C_{16}H_{19}O_7N_2Br$ . Calculated %: C 44.55; H 4.44; N 6.50; Br 18.52.

o-Bromo-p-aminobenzylacetylaminomalonic ester (IVb). Hydrogenation of 0.8 g of (IIIb) with 0.9 g of skeletal nickel in 10 ml of 95% alcohol for 50 minutes at 45-50°C gave 0.65 g (87%) of substance. Colorless prismatic crystals with m.p. 166-167°C (from alcohol).

Found %: C 47.99; H 5.87; N 7.36; Br 19.46.  $C_{16}H_{21}O_5N_2Br$ . Calculated %: C 47.89; H 5.28; N 6.98; Br 19.92.

o-Bromo-p-di-(2-hydroxyethyl)-aminobenzylacetylaminomalonic ester (Vb). From 0.65 g (0.00162 mole) of (IVb) in 4 ml of 50% acetic acid and 2 ml (0.0436 mole) of ethylene oxide we obtained 0.55 g (70%) of substance with m.p. 116-118°C (from benzene).

The substance showed dimorphism. After recrystallization from dry ether we obtained colorless needles with m.p. 88.5-89.5°C.

Found %: C 49.32; H 5.97; N 5.80; Br 15.84.  $C_{20}H_{29}O_7N_2Br$ . Calculated %: C 49.43; H 5.97; N 5.73; Br 16.32.

After recrystallization from benzene the same substance had m.p. 119-120.5°C; from analytical data it did not differ from that described above and on further recrystallization from ether again acquired the m.p. 88.5-89.5°C.

o-Bromo-p-di-(2-Chloroethyl)-aminobenzylacetylaminomalonic ester (VIb). Just as in preparing (VIa), boiling 0.55 g (0.00112 mole) of (Vb) with 0.8 ml (0.0112 mole) of thionyl chloride in 6 ml of dry chloroform gave 0.5 g (84%) of substance with m.p. 152.5-154°C. Three recrystallizations from alcohol gave colorless needles with m.p. 157-158°C.

Found %: C 46.09; H 5.39; N 5.36.  $C_{20}H_{17}O_5N_2Cl_2Br$ . Calculated %: C 45.98; H 5.17; N 5.33.

A mixed sample of (VIb) with its analog (VIa) had m.p. 158.5-159°C, melting without depression of the melting point.

Hydrochloride of o-bromo-p-di-(2-chloroethyl)-amino-*dl*-phenylalanine ("o-bromosarcosylsin") (VIIb). Analogously to the preparation of (VIIa), from 0.38 g of (VIb) we obtained 0.18 g (60%) of substance with m.p. 182-184°C (decomposition), a white, crystalline powder, moderately soluble in water, better in alcohol, and insoluble in the usual organic solvents.

Found %: C 37.28; H 4.97; N 6.39.  $C_{13}H_{17}O_2N_2Cl_2Br \cdot HCl$ . Calculated %: C 37.12; H 4.31; N 6.66.

#### SUMMARY

1. Starting from chloro-p-nitrotoluene through o-chloro-p-nitrobenzyl bromide, o-chloro-p-nitrobenzylacetylaminomalonic ester, o-chloro-p-aminobenzylacetylaminomalonic ester, o-chloro-p-di-(2-hydroxyethyl)benzyl-aminoacetylaminomalonic ester, and o-chloro-p-di-(2-chloroethyl)-aminobenzylacetylaminomalonic ester we have synthesized o-chloro-p-di-(2-chloroethyl)-amino-*dl*-phenylalanine ("o-chlorosarcosylsin").

From o-bromo-p-nitrotoluene by the same scheme we have prepared o-bromo-p-di-(2-chloroethyl)-amino-*dl*-phenylalanine ("o-bromosarcosylsin").

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. Some or all of this periodical literature may well be available in English translation. A complete list of the cover-to-cover English translations appears at the back of this issue.

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# THE SYNTHESIS AND PROPERTIES OF SOME DERIVATIVES OF $\beta$ -PHENYLALANINE

## II. SYNTHESIS OF $\beta$ -(p-DIMETHYLAMINOPHENYL)-D, L-ALANYL-D, L-ALANINE AND ITS N-OXIDE

B. L. Moldaver and Z. V. Pushkareva

Sverdlovsk Research Institute for Poliomyelitis Prophylaxis

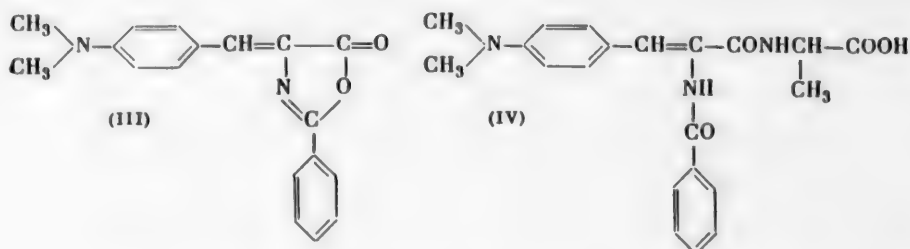
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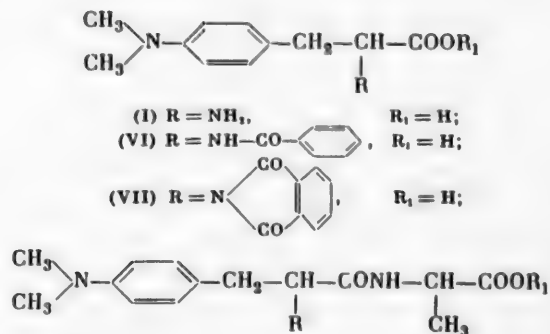
In the previous communication [1] we described the synthesis and some properties of derivatives of p-dimethylaminophenylalanine (I) for biological study. The present work is devoted to the synthesis of more complex derivatives of this series.

For the synthesis of p-dimethylaminophenylalanyl-alanine (II)\* we used the azolactone of  $\alpha$ -benzoylamino-p-dimethylaminocinnamic acid [2] (III). In the reaction of the latter at room temperature with an equimolecular amount of alanine in the presence of alkali in aqueous acetone we obtained  $\alpha$ -benzoylamino-p-dimethylaminocinnamoylalanine (IV) with a 10% yield.

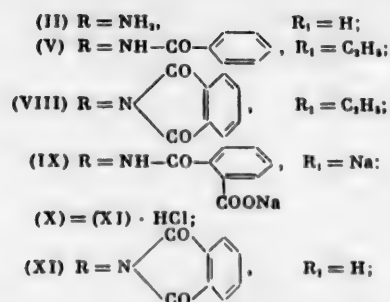


The yield was increased to 96% with excess alanine and boiling of the reaction mass. This unsaturated dipeptide showed unusual stability of the double bond toward hydrogenation. Only by hydrogenation in the presence of palladium black did we obtain a product on hydrolysis of which by acid was there found by paper chromatography a small amount of p-dimethylaminophenylalanine. (I).

The saturated peptide was obtained as the ethyl ester of  $\alpha$ -benzoyl-p-dimethylaminophenylalanyl-alanine (V) by condensation of  $\alpha$ -benzoyl-p-dimethylaminophenylalanine [1] (VI) with alanine ethyl ester [3] in the presence of dicyclohexylcarbodiimide [4]. Since the benzoyl residue is difficult to split off without destroying the peptide bond, compound (V) is unsuitable for the isolation of the free dipeptide (II). The latter was synthesized using the phthalyl residue for protecting the amino group.



\* We used only the racemic compound in this work.



The N-phthalyl-p-dimethylaminophenylalanine (VII) needed for synthesis of the peptide was obtained by fusing equimolecular amounts of p-dimethylaminophenylalanine (I) and phthalic anhydride. On condensation of compound (VII) with alanine ethyl ester in the presence of dicylohexylcarbodiimide [4] we obtained the ethyl ester of N-phthalyl-p-dimethylaminophenylalanyl-alanine (VIII). Boiling ester (VIII) with excess  $Na_2CO_3$  in water for six hours led to saponification of the ester and splitting of the N-phthalyl ring with formation of the disodium salt of N-o-carboxybenzoyl-p-dimethylaminophenylalanyl-alanine (IX), as was demonstrated by potentiometric titration of this salt.

Saponification of the ester bond with retention of the N-phthalyl ring was successful [5] by the action of 18 % HCl on the ester (VIII) at a temperature of 75-80°C. Here we obtained a 75% yield of hydrochloride of N-phthalyl-p-dimethylaminophenylalanyl-alanine (X). From the hydrochloride (X) we isolated by the use of triethylamine N-phthalyl-p-dimethylaminophenylalanyl-alanine (XI). For splitting the N-phthalyl group from this compound we used the method of Schuman [6] \* which was first studied on N-phthalyl-p-dimethylaminophenylalanine (VII). On treating the latter with phenylhydrazine in the presence of triethylamine, we isolated the free amino acid (I). Under the same conditions from the N-phthalyl derivative of dipeptide (XI) we obtained p-dimethylaminophenylalanyl-alanine (II) in the form of white crystals with m.p. 265°C. As the chromatogram shows, (Fig. 1), the substance on hydrolysis gives p-dimethylaminophenylalanine and alanine. p-Dimethylaminophenylalanyl-alanine (II) was also obtained on treatment of the disodium salt of N-o-carboxybenzoyl-p-dimethylaminophenylalanyl-alanine (IX) with excess hydrochloric acid (pH 1.5, 24 hour maintenance at 20°C). Along with the splitting off of the N-o-carboxybenzoyl group there was partial destruction of the peptide bond, which was shown chromatographically.



Fig. 1. Chromatogram of the dipeptide (a) and its hydrolyzate (b) in the presence of standards: Alanine (c) and p-dimethylaminophenylalanine (d).

\* With replacement of tributylamine by triethylamine.

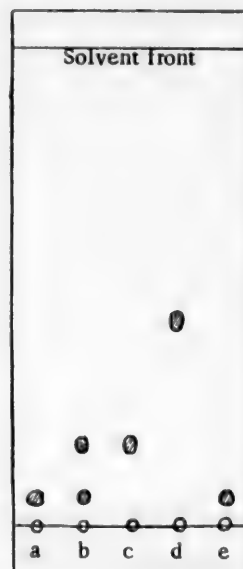
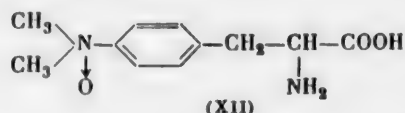


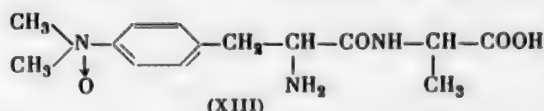
Fig. 2. Chromatogram of N-oxide of the dipeptide (a) and its hydrolyzate (b) in the presence of standards: Alanine (c), p-dimethylamino-phenylalanine (d), and p-dimethylaminophenylalanine N-oxide (e).

p-Dimethylaminophenylalanine N-oxide (XII) was previously obtained with preliminary protection of the  $\alpha$ -amino group by an acyl residue [1].



Considering the data of O. L. Legedev and co-workers [7], we tried to obtain p-dimethylaminophenylalanine N-oxide by direct oxidation of this amino acid. We showed that on 20 hour stirring in water of equimolecular amounts of p-dimethylaminophenylalanine and pertungstic acid in the presence of Trilon B there is almost quantitative formation of p-dimethylaminophenylalanine N-oxide.

Under analogous conditions we obtained p-dimethylaminophenylalanyl alanine N-oxide (XIII). The structure of the latter was confirmed by paper chromatography of its hydrolyzate (Fig. 2).



The properties of both the dipeptide (II) and its N-oxide (XIII) are determined chiefly by the p-dimethylaminophenylalanine part of the molecule. Thus, the  $R_f$  value and the melting point of the dipeptide (0.39 and 265°C respectively) and its N-oxide (0.05 and 172-175°C) are very close to the values of p-dimethylaminophenylalanine (0.43 and 263°C) and its N-oxide (0.05, 192°C). Also, the N-oxide of the dipeptide (XIII), like the N-oxide of p-dimethylaminophenylalanine (XII) has the characteristic of forming a hydrate which loses water only with difficulty.

#### EXPERIMENTAL\*

$\alpha$ -Benzoylamino-p-dimethylaminochinamoylalanine (VI). A mixture of 1.46 g (0.005 mole) of azolactone of  $\alpha$ -benzoylamino-p-dimethylaminocinnamic acid (III), 0.44 g (0.005 mole) of alanine, and 0.2 g (0.005 mole) of sodium hydroxide with 5 ml of water and 15 ml of acetone was shaken at room temperature for ten hours. The precipitate of azolactone was filtered off, the filtrate was acidified with hydrochloric acid to pH 4.0, the precipitate which came down was filtered off and twice recrystallized from methanol and aqueous alcohol to give yellow needles with m.p. 128-132°C. Yield 0.2 g (10.5 %). In paper chromatography of the hydrolyzate of the substance (four hour heating on a boiling water bath with 18% HCl) we found one ninhydrin positive spot with the  $R_f$  of alanine.

At a ratio of azolactone, alanine, and sodium hydroxide of 1 : 3 : 3 and boiling the reaction mixture for one hour, the yield of the substance was 96%.

Found %: C 62.95, 63.08; H 6.56, 6.23; N 10.35, 10.43.  $C_{21}H_{23}O_4N_3 \cdot H_2O$ . Calculated %: C 63.14; H 6.31; N 10.52.

Ethyl ester of  $\alpha$ -benzoyl-p-dimethylaminophenylalanyl-alanine (V). A solution of 0.624 g (0.002 mole) of  $\alpha$ -benzoyl-p-dimethylaminophenylalanine (VI), 0.234 g (0.002 mole) of alanine ethyl ester, and 0.412 g (0.002 mole) of dicyclohexylcarbodiimide in 15 ml of dry chloroform was stirred for 30 minutes and the mixture left overnight at room temperature. The filtrate after separation of dicyclohexyl urea was evaporated dry and the residue was recrystallized from alcohol, forming 0.47 g (57%) of a white, crystalline substance with m.p. 159-160°C.

Found %: C 67.04; H 7.12; N 10.42.  $C_{23}H_{29}O_4N_3$ . Calculated %: C 67.2; H 7.06; N 10.20.

By paper chromatography of the hydrolyzate of the substance (30 minute boiling with concentrated HCl) found two ninhydrin positive spots with  $R_f$  of alanine and p-dimethylaminophenylalanine.

N-Phthalyl-p-dimethylaminophenylalanine (VII). We fused 4.0 g (0.019 mole) of p-dimethylaminophenylalanine with 2.88 g (0.019 mole) of phthalic anhydride for 15 minutes at bath temperature from 130 to 160°C. The melt was dissolved in 150 ml of boiling alcohol, 150 ml of water was added, and on slow cooling we obtained 5.1 g (78.5%) of a yellow, crystalline substance (prisms) with m.p. 200-201°C.

\* All the melting points are uncorrected. Chromatography in all cases was carried out under conditions described in paper [1].



Found %: C 67.67, 67.14; H 5.45, 5.35; N 8.69, 8.73.  $C_{19}H_{19}O_4N_2$ ; Calculated %: C 67.42; H 5.35; N 8.27.

A solution of 1.0 g (0.003 mole) of N-phthalyl-p-dimethylaminophenylalanine (VII), 0.64 g (0.006 mole) of phenylhydrazine, and 0.3 g (0.003 mole) of triethylamine in 8 ml (0.003 mole) of glacial acetic acid and 20 ml of methylethyl ketone and cooling of the solution, a white precipitate came down. Weight 0.2 g (33%), m.p. 250°C (decomposition). In paper chromatography we found one ninhydrin positive spot with  $R_f$  of p-dimethylaminophenylalanine.

Ethyl ester of N-phthalyl-p-dimethylaminophenylalanyl-alanine (VIII). a) A solution of 5.0 g of N-phthalyl-p-dimethylaminophenylalanine (VII), 3.05 g of dicyclohexylcarbodiimide, and 1.7 ml of alanine ethyl ester (equimolecular amounts) in 100 ml of dry chloroform was treated in the same way as in preparing compound (V). We obtained 3.5 g (54.2%) of a white crystalline substance (needles joined in the form of a "palm leaf") with m.p. 150-151°C.

Found %: C 65.72, 66.19; H 6.18, 6.18; N 9.84, 10.16.  $C_{24}H_{27}O_5N_3$ . Calculated %: C 65.89; H 6.22; N 9.6.

b) The components were taken under the same conditions, but the alanine ethyl ester was prepared from the corresponding hydrochloride by addition of triethylamine to an alcohol solution of the hydrochloride and precipitation of triethylamine hydrochloride with absolute ether. In the ether-alcohol filtrate we dissolved the dicyclohexylcarbodiimide and suspended compound (VII). The resulting precipitate after two hours was freed from dicyclohexyl urea and recrystallized from alcohol, forming a yellow crystalline substance (large, short prisms) with m.p. 156-157°. Yield 48.7%.

Found %: C 66.20, 66.23; H 6.27, 6.26.  $C_{24}H_{27}O_5N_3$ . Calculated %: C 65.89; H 6.22.

N-Phthalyl-p-dimethylaminophenylalanyl-alanine hydrochloride (X). We dissolved 2.19 g of the ethyl ester of N-phthalyl-p-dimethylaminophenylalanyl-alanine (IV) in 5 ml of 18% HCl and kept the solution for 10-12 minutes at 75-80°C, and then placed it for 40 hours in a vacuum desiccator over  $CaCl_2$  and KOH. The dry residue was crystallized from 8 ml of methanol, forming 1.52 g (74%) of a white crystalline substance with m.p. 212-213°C (decomposition).

Found %: C 59.37; H 5.59; N 9.37.  $C_{22}H_{23}O_5N_3 \cdot HCl$ . Calculated %: C 59.25; H 5.43; N 9.42.

In potentiometric titration of 0.046 g of substance 2.07 ml of 0.1 N NaOH was used.

N-Phthalyl-p-dimethylaminophenylalanyl-alanine (XI). To a solution of 0.265 g (0.0006 mole) of hydrochloride (X) in 4 ml of water was added 0.082 ml (0.0006 mole) of triethylamine. The precipitate was filtered off. Weight 0.2 g (82%). After recrystallization from aqueous alcohol, m.p. 173-176°C (at 125-130°C the substance sintered).

Found %: C 64.08, 64.05; H 5.93, 5.92.  $C_{22}H_{23}O_5N_3$ . Calculated %: C 64.48; H 5.69.

p-Dimethylaminophenylalanyl-alanine (II). a) The previous compound (XI) was treated with phenylhydrazine under the conditions described above for N-phthalyl-p-dimethylaminophenylalanine (VII). We obtained 43.8% of a white, crystalline substance with m.p. 265°C (with formation of a red melt). Under the microscope, fine rhombic plates were seen. In paper chromatography the water solution of the substance showed one ninhydrin positive spot with  $R_f$  0.39. In chromatography of the hydrolyzate of the substance (30 minute boiling in concentrated HCl) two ninhydrin positive spots were observed, with the  $R_f$  of alanine and p-dimethylaminophenylalanine (Fig. 1). For analysis, the substance was dried in a vacuum over  $P_2O_5$ .

Found %: C 59.91, 60.43; H 7.27, 7.52; N 15.34.  $C_{14}H_{21}O_3N_3$ . Calculated %: C 60.2; H 7.23; N 15.03.

b) A mixture of 3.5 g of ethyl ester of N-phthalyl dipeptide (VIII) 3.5 g of  $Na_2CO_3$ , and 35 ml of water was boiled under reflux, for six hours. Addition of 180 ml of alcohol to the resulting solution precipitated  $Na_2CO_3$ , and the filtrate was evaporated dry. After repeated purification from admixed  $Na_2CO_3$  by resolution in anhydrous alcohol and evaporation of the filtrate, we obtained a white crystalline substance with m.p. 218-219°C (decomposition) (IX). The yield was quantitative. In potentiometric titration of 0.203 g of the substance we used 2.67 ml of 0.5N HCl, which corresponded to 3 equivalents of acid.

A solution of 0.4 g of the resulting salt in 8 ml of 0.5 N HCl stood at room temperature for 24 hours, and then was carefully evaporated dry. The residue was dissolved in anhydrous alcohol, the solution was filtered, the filtrate



was evaporated, and the resulting residue, dissolved in water, was made alkaline by anionite EDE-10P to pH 4.8-5.2. After distillation of the water, we obtained 0.04 g (15.4%) of substance with m.p. 265°C (from 80% alcohol), identical with that described above (product of "a").

p-Dimethylaminophenylalanine N-oxide (XII). A mixture of 0.5 g (0.0024 mole) of p-dimethylaminophenylalanine, 0.27 ml of 30% aqueous  $H_2O_2$ , (0.0024 mole), 0.03 g of tungstic acid (0.00012 mole) and 1 mg of Trilone B was stirred in 10 ml of water at room temperature for 24 hours. The resulting solution after treatment with activated charcoal or 5% Pd/C was evaporated in a vacuum to small volume and stirred with excess anhydrous alcohol. We isolated 0.4 g of substance with m.p. 178°C (decomposition). After recrystallization from a mixture of 90% aqueous alcohol and ether, m.p. 192°C (decomposition).

For analysis, the substance was dried over  $P_2O_5$ .

Found %: C 54.96, 54.82; H 7.42, 7.41;  $H_2O$  8.2  $C_{11}H_{16}O_3N_2 \cdot H_2O$ . Calculated %: C 54.5; H 7.48;  $H_2O$  8.03.

After drying in a vacuum over  $P_2O_5$  at 80°C for four hours

Found %: C 58.89; H 7.26; N 12.65.  $C_{11}H_{16}O_3N_2$ . Calculated %: C 58.9; H 7.2; N 12.5.

Chromatography of the pure substance and identity of the N-oxide were described previously [1].

p-Dimethylaminophenylalanyl-alanine N-oxide (XIII) was obtained from the dipeptide (II) as with the preceding compound, in the form of a pinkish crystalline substance with m.p. 172-175°C (decomposition)

Found %: C 53.98; H 7.49;  $C_{14}H_{21}O_4N_3 \cdot H_2O$ . Calculated %: C 53.75; H 7.36.

In paper chromatography of a water solution of the substance we found one ninhydrin positive spot,  $R_f$  0.05. On chromatography of the hydrolyzate of the substance (30 minute boiling with concentrated HCl) we found two spots with the  $R_f$  of p-dimethylaminophenylalanine N-oxide and alanine (Fig. 2).

#### SUMMARY

1. We have described the preparation of p-dimethylaminophenylalanylalanine and its derivatives.
2. We have obtained p-dimethylaminophenylalanine N-oxide and p-dimethylaminophenylalanyl-alanine N-oxide by oxidation of the free amino acid and dipeptide with pertungstic acid.

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## PREPARATION OF $\delta$ -N-GUANYL-GRAMICIDIN S

V. M. Stepanov and A. B. Silaev

M. V. Lomonosov Moscow State University

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Chemical modification is an important method for studying the relation between chemical structure and biological activity of antibiotics. This method has often been applied to the antibiotic-cyclopeptidegramicidin S [1-4]. The preparation of various derivatives of gramicidin S and the subsequent comparison of the activity of the modified preparations with that of the starting antibiotic permit an explanation of the structural elements of the antibiotic which are responsible for the biological activity, and establish the degree of specificity of the molecule. As a rule, the  $\delta$ -amino group of ornithine undergoes modification, since it is the sole free functional group in the molecule of gramicidin S. The present work is devoted to the conversion of this group into guanyl.

The literature indicates that the antibiotic activity of gramicidin S is closely connected with its basic properties. Destruction of the basic properties leads to loss of activity. The guanidyl group is a considerably stronger base than the amino. Therefore a comparison of the antibacterial activity of gramicidin S with that of S-N-guanyl-gramicidin S can explain how strengthening the basic properties of the antibiotic will affect its biological activity. On the other hand, in guanylation of gramicidin S there is a replacement of the L-ornithine residue by L-arginine. This permits us to show whether the presence of the "unusual" amino acid, L-ornithine, is specific for gramicidin S as an antibiotic.

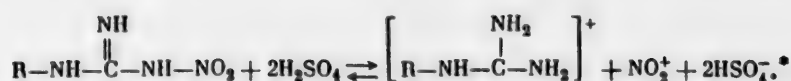
We first tried to guanylate gramicidin S by the method usually used for this purpose with S-methylisothiourea [5]. Here there occurred formation of  $\delta$ -N-guanyl-gramicidin S as was indicated by the appearance of a sharp Sakaguchi reaction. However, in spite of the use of different conditions, we could not obtain  $\delta$ -N-guanyl-gramicidin S free from contamination by unreacted gramicidin S. Our product invariably gave a clear reaction with ninhydrin which showed the presence of gramicidin S. Separation of the mixture of gramicidin S and  $\delta$ -N-guanyl-gramicidin S was especially difficult, since both substances are bases and have similar physicochemical properties. Exactly the same result was obtained in a guanylation of gramicidin S by O-methylisourea, although this reagent is considered a very active guanylation agent [6].

It is interesting to note that M. P. Znamenskaya and A. N. Belozerskii who guanylated gramicidin S with S-methylisothiourea in an alkaline medium met with the same difficulty [7]. The use of two guanylations gave them a mixture which contained about 70% guanyl-gramicidin S and 30% of the starting antibiotic.

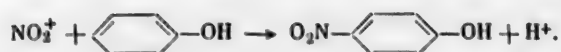
It is easy to see that the difficulty which occurs in attempts to prepare pure  $\delta$ -N-guanyl-gramicidin S by the usual process is inherent in the method and depends on the one step process of conversion of the amino group into the guanidine. If the reaction cannot be carried out quantitatively, a mixture of reaction products will be formed and the starting amino compound, because of its similarity in properties, cannot practically be separated. Starting from this idea, we decided to seek another process for conversion of the amino compound into the corresponding guanidine which would take place through a neutral substance, since in this case the difficulty connected with separation of pure reaction product would disappear of itself.

A suitable intermediate compound for the synthesis of  $\delta$ -N-guanylgramicidin S was  $\delta$ -N-nitroguanyl-gramicidin S, which we prepared in 87% yield by the action of N-methyl-N-nitroso-N'-nitroguanidine on gramicidin S. This reaction occurs smoothly even at room temperature and the resulting substance is practically insoluble in most solvents and can be easily separated in the pure state. The synthesis of substituted guanidines from amines using N-methyl-N-nitroso-N'-nitroguanidine was worked out by McKay [8] and was first extended to peptides by us [3].

Denitration of  $\delta$ -N-nitroguanyl-gramicidin S to obtain  $\delta$ -N-guanyl-gramicidin S can be carried out by two methods. In one of these we used the reverse reaction of the nitration of guanidine. On solution of  $\delta$ -N-nitroguanyl-gramicidin S in concentrated sulfuric acid an equilibrium occurs:



It is easy to introduce into this system an irreversibly nitrated compound such as phenol or salicylic acid, which shifts the equilibrium completely to the side of formation of  $\delta$ -N-guanyl-gramicidin S, since the nitro cation is gradually used up in nitrating the compound added to the mixture as it is a nitro group acceptor:



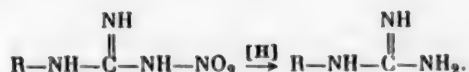
This reaction, the so-called transnitration [9], has not previously been used as a preparative method. We have been able to use it for obtaining  $\delta$ -N-guanyl-gramicidin S.

We have carried out transnitration by dissolving  $\delta$ -N-nitroguanylgramicidin S in a mixture of anhydrous formic acid with a large excess of phenol and by adding to this solution concentrated sulfuric acid so calculated that its final concentration was not less than 85-90 %. The reaction took place at low temperatures so as to avoid decomposition of the nitroguanidine group. After treatment of the reaction mixture we succeeded in obtaining  $\delta$ -N-guanyl-gramicidin S with a yield of 60-67%.

It is necessary to note that denitration of  $\delta$ -N-nitroguanylgramicidin S can occur on solution in sulfuric acid and without addition of phenol or salicylic acid. In this case the role of nitro group acceptor is played by the aromatic ring of the phenylalanine in the gramicidin. To avoid this, it is necessary first, before solution of the  $\delta$ -N-nitroguanyl-gramicidin S to add to the mixture a large excess of the compound which serves as the nitro group acceptor.

The resulting  $\delta$ -N-guanyl-gramicidin S does not contain an admixture of gramicidin S. It was characterized by elementary analysis. The paper chromatography method showed that the  $\delta$ -N-guanyl-gramicidin S contained leucine, valine, phenylalanine, proline, and arginine.

Aside from the reaction of transnitration we can use for the preparation of  $\delta$ -N-guanyl-gramicidin S hydrogenolysis of the N-NO<sub>2</sub> bond as discovered by M. Bergmann [10].  $\delta$ -N-Nitroguanyl-gramicidin S dissolved in anhydrous formic acid was hydrogenated at room temperature and atmospheric pressure, after which we isolated 70% of  $\delta$ -N-guanylgramicidin S formate.



We used palladium as the catalyst for the hydrogenation. The more suitable experimental conditions for this reaction were described previously by us [3].

Study of the antibacterial action of  $\delta$ -N-guanyl-gramicidin S was carried out by A. N. Polin, to whom the authors express thanks. He showed that this derivative sometimes yielded somewhat in activity to the starting gramicidin S (bacteriostatic action on *Bacterium coli* and *Klebsiella pneumoniae*). In other cases the activity of both compounds was equal (*Staphylococcus aureus* and *Bacterium mycoides*). Gramicidin S and its guanidine derivative inhibit the absorption of oxygen by cells of *Staphylococcus aureus* to the same extent at a concentration of 1.5  $\mu\text{g}/\text{ml}$  [11].

Thus, replacement in gramicidin S of the free amino group by guanidine and the linked with this conversion of the L-ornithine residue into L-arginine scarcely affect the antibacterial action. This indicates that the presence in the structure of gramicidin S of an amino acid "unusual" for proteins, such as ornithine, is, in general, not necessary for antibiotic activity.

The function of the free amino group in gramicidin S is that it gives basic properties to the antibiotic. In this respect the guanidine group fully replaces the amino group in gramicidin S which explains the retention of activity.

\* Here for simplicity we write only half a molecule of gramicidin S in the form R-NH<sub>2</sub>, where R denotes the molecule of gramicidin S without the  $\delta$ -amino group of ornithine. It should be remembered that there are two such groups in gramicidin S.

## EXPERIMENTAL

**$\delta$ -N-Nitroguanyl-gramicidin S.** To a weight of 3.5 g (24 mmole) of N-methyl-N-nitroso-N'-nitroguanidine in 15 ml of ethyl alcohol was added a solution of 6.5 g (10 m-equiv) of gramicidin S hydrochloride in 50 ml of ethyl alcohol and 11 ml of 1 N sodium hydroxide. There was violent evolution of gas, the solution rapidly became cloudy and a very fine precipitate formed. After 15 hours the solution was heated to boiling on a water bath, cooled, and filtered. The precipitate was washed successively with 20 ml of alcohol, 10 ml of acetone, and 20 ml of ether. After drying it over sulfuric acid, we obtained 5.86 g of substance. Yield 87%. The ninhydrin reaction was negative. M.p. 272-275°C (with decomposition). The substance did not dissolve in water and was insoluble or very poorly soluble in alcohol, acetone, ether, chloroform, dioxane, acetic acid, and anisole; it dissolved well in anhydrous formic acid and still better in phenol. The solution in concentrated sulfuric acid gave a blue color with diphenylamine (reaction for nitrate). For analysis the substance was recrystallized from a mixture of formic acid and acetone.

Found %: C 55.66, 55.30; H 7.48, 7.40; N 18.77, 18.63.  $C_{62}H_{94}O_{14}N_{18} \cdot 2H_2O$ . Calculated %: C 55.08; H 7.31; N 18.63.

In view of the insolubility of the substance we could not carry out paper electrophoresis.

**$\delta$ -N-Guanyl-gramicidin S (obtained by transnitration using phenol).** We dissolved 728 mg (1.1 m-equiv.) of  $\delta$ -N-nitroguanylgramicidin S at 40°C in a mixture of 1.5 g (16 mmole) of freshly distilled phenol and 2 ml of anhydrous formic acid. We added to the solution, cooled to -10°C, 10 ml of concentrated sulfuric acid. The rate of addition of sulfuric acid and the intensity of cooling the mixture was so regulated that the reaction temperature of the mixture did not exceed +5°C. We usually kept the reaction temperature in the range from -5 to 0°C. However, sometimes phenol crystallized and the temperature was raised or a further 2-3 ml of anhydrous formic acid was added. The solution was stirred for 1.5 hours longer. The temperature rose to 15°C, marked evolution of gas, bubbles began and the solution became a dark orange color. Then the solution was poured with stirring onto 100 g of cracked ice. Forty ml of ether was added to the mixture to remove phenol. The precipitate which formed was filtered off and treated on the filter with several portions of ether (250 ml in all). We obtained 800 mg of powdery substance. For purification it was dissolved in 4 ml of hot methanol and reprecipitated with water. We obtained 496 mg of white, finely crystalline substance. M.p. 290-294°C (decomposition). From the nitrogen content (Kjeldahl) the substance was the acid sulfate of  $\delta$ -N-guanyl-gramicidin S.

Found %: N 15.24, 15.41.  $C_{62}H_{96}O_{10}N_{16} \cdot 2H_2O \cdot 2H_2SO_4$ . Calculated %: N 15.42.

The results of a study of this substance by paper electrophoresis (30% acetic acid, 220 V, six hours, length of paper strip 34 cm) are given in the table.

For full analysis, the acid sulfate of  $\delta$ -N-guanyl-gramicidin S was converted to the hydrochloride. We dissolved 160 mg of guanyl-gramicidin S acid sulfate in 10 ml of chloroform. The solution was treated with 10 ml of 1 N sodium hydroxide, the chloroform layer was separated and washed with water, and then 10 ml of 5 N hydrochloric acid. The chloroform layer was evaporated dry at room temperature and gave 118 mg of  $\delta$ -N-guanyl-gramicidin S hydrochloride. M.p. 292-295°C (decomposition).

Found %: C 56.16; 55.86; H 7.83, 7.94; N 16.36, 16.33.  $C_{62}H_{96}N_{16}O_{10} \cdot 2H_2O \cdot 2HCl$ . Calculated %: C 55.75; H 7.70; N 16.77.

For purification the  $\delta$ -N-guanyl-gramicidin S obtained by transnitration and converted into its hydrochloride could be treated with sulfocationite KU-2. The unpurified  $\delta$ -N-guanyl-gramicidin S acid sulfate obtained by the above method from 430 mg of  $\delta$ -N-nitroguanylgramicidin S was dissolved in a mixture of 4 ml of methanol and 1 ml of chloroform. The solution was passed at a rate of 6 ml/hour through a column with resin KU-2 (height 200 mm, diameter 9 mm). The resin was first converted to the  $H^+$  form and carefully washed with methanol. After sorption of the  $\delta$ -N-guanyl-gramicidin S by the cationite, the column was again washed with methanol.  $\delta$ -N-guanyl-gramicidin S was eluted with 2 N HCl in methanol (70 ml). After evaporation of the eluate in a vacuum we obtained 287 mg of  $\delta$ -N-guanyl-gramicidin S hydrochloride.

**$\delta$ -N-Guanyl-gramicidin S (obtained by transnitration with use of salicylic acid).** We dissolved 420 mg (0.64 m-equiv.) of  $\delta$ -N-nitroguanyl-gramicidin S with slight heat in 4 ml of anhydrous formic acid. To the solution cooled to -4°C with stirring and cooling we added a solution of 440 mg (3.2 mmole) of salicylic acid in 10 ml of concentrated sulfuric acid. After standing for one hour at room temperature the mixture was poured into a beaker with 60 g of ice and 20 g of water. We added 20 ml of ether. A flakey precipitate formed between the two layers; it was filtered

Results of Electrophoresis of a Preparation of  $\delta$ -N-Guanyl-gramicidin S

Name of substance	Process of detection	Distance of spot from point of deposition (shift to cathode)
Gramicidin S . . . . .	Ninhydrin	6.1 cm
Gramicidin S . . . . .	Sakaguchi reaction	Not detected
$\delta$ -N-Guanyl-gramicidin S . . . . .	Ninhydrin	Not detected
$\delta$ -N-Guanyl-gramicidin S . . . . .	Sakaguchi reaction	6.2 cm

off, washed with water to disappearance of acid reaction in the wash water, and washed several times with ether. After drying at 105°C it gave 379 mg of  $\delta$ -N-guanyl-gramicidin S acid sulfate. Yield 80%. M.p. 292-294°C (decomposition). The substance contained a trace of salicylic acid. On paper ionophoresis it behaved in the same way as the preparation obtained by transnitration using phenol.

## SUMMARY

1. We have synthesized  $\delta$ -N-guanyl-gramicidin S.
2. We have suggested the use of the transnitration reaction for conversion of the nitroguanidino compound to the corresponding guanidine.
3. We have shown the possibility of passing from an amino compound to a guanidino compound through the nitroguanidine.
4. The antibiotic properties of  $\delta$ -N-guanyl-gramicidin S and gramicidin S are similar.

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## THE PREPARATION OF PHENYL SUBSTITUTED DERIVATIVES OF GRAMICIDIN S

V. M. Stepanov and A. B. Silaev

M. V. Lomonosov Moscow State University

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As is known, a large number of derivatives of gramicidin S have been synthesized at the  $\delta$ -amine group of the ornithine. Study of their properties has permitted definite conclusions as to the significance of the free amino group for the biological activity of gramicidin S [1-6]. Modification of other parts of the molecule of gramicidin S has scarcely been carried out.

After the free amino group of the ornithine the most active structural element of gramicidin S in chemical respects is the aromatic ring of the D-phenylalanine. Obtaining derivatives in which the aromatic ring of the phenylalanine would be modified is of great interest, since the biological activity of gramicidin S has often been ascribed to the presence of the unusual "unnatural" D-phenylalanine.

Considering the well known chemical stability of gramicidin S, we have used nitration for modification of the aromatic ring. At first we nitrated gramicidin S by the action of ammonium nitrate in concentrated sulfuric acid [7]. As would be expected, gramicidin S was easily nitrated under these conditions, but the reaction product invariably gave a distinct Yanovskii reaction for dinitro compounds [8]. Apparently under these conditions, gramicidin S in large measure was partly converted to Ph-dinitrogramicidin S\*.

This led us to use somewhat milder conditions of nitration. For obtaining Ph-nitrogramicidin S, gramicidin S was dissolved in concentrated sulfuric acid and treated in the cold with concentrated nitric acid. We obtained an 82 % yield of Ph-nitrogramicidin S which did not now give the Yanovskii reaction. As experiment showed, when gramicidin S was nitrated it was not necessary to protect the amino group of ornithine; it was enough merely to take measures to avoid deamination of gramicidin S by oxides of nitrogen (low temperature, use of nitric acid which did not contain oxides of nitrogen, addition of urea).\*\*

For preparation of Ph-nitrogramicidin S, we chose as the reduction method catalytic hydrogenation over palladium [9]. Ph-aminogramicidin S was obtained in 68 % yield and was characterized as the dipicrate. This derivative of gramicidin S in addition to the two aliphatic amino groups of ornithine also had two aromatic amino groups of the aminophenylalanines, which led to a small increase in electrophoretic mobility in acid medium as compared to gramicidin S. The aromatic amino groups were easily diazotized. It is very interesting that Ph-aminogramicidin S is easily soluble in water.

Our Ph-aminogramicidin S differed strongly in a number of properties from the reduction product of Ph-nitrogramicidin S with zinc dust or titanium trichloride described by M.P. Znamenskaya and A. N. Belozerskii [2]. However, these authors themselves did not call the product which they synthesized aminogramicidin.

In order to show that in the course of nitration of gramicidin S, followed by reduction of the nitro group, only the benzene ring of the D-phenylalanine residue is changed, we eliminated the aromatic amino groups of Ph-aminogramicidin S. Ph-aminogramicidin S was diazotized with the calculated amount of sodium nitrite in hydrochloric acid. The resulting solution of diazo compound was treated in the cold with a great excess of calcium hypophosphite. The substance which resulted from this elimination of the aromatic amino group did not differ from gramicidin S in chemical properties or antibiotic activity. Thus, in obtaining the above mentioned ph-substituted derivative of gramicidin S, the cyclopeptide skeleton of the antibiotic molecule remained unaffected.

\* Here and later phenyl substituted derivatives of gramicidin S will be designated Ph-.

\*\* We must mention that in 1957 M.P. Znamenskaya and A.N. Belozerskii described the preparation of nitrogramicidin S by nitration of gramicidin S with nitric acid in a medium of acetic acid [2].



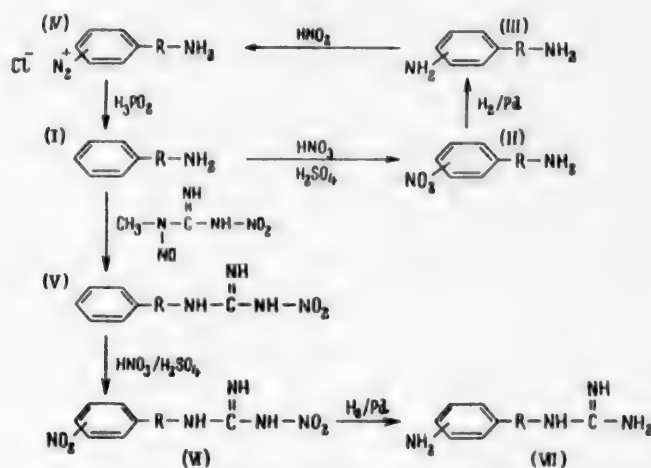
We synthesized derivatives of gramicidin S in which substitution in the aromatic ring of phenylalanine was coupled with guanidation of the  $\delta$ -amino group of the ornithine.

We have previously noted [6] that on solution of  $\delta$ -N-nitroguanylggramicidin S in concentrated sulfuric acid there is denitration of the nitroguanidine group because of the irreversible transfer of N-nitro groups to phenylalanine. For completion of the nitration of the phenylalanine residue we added concentrated nitric acid to the solution, upon which there occurred repeated nitration of the guanidine group. As a result of this reaction we obtained a 95% yield of Ph-nitro- $\delta$ -N-nitroguanylggramicidin S. This substance like the  $\delta$ -N-nitroguanylggramicidin S was distinguished by very poor solubility in most solvents and could easily be obtained pure; it was a suitable intermediate product for the synthesis of other derivatives of gramicidin S.

On catalytic hydrogenation over palladium in a mixture of formic and hydrochloric acids, Ph-nitro- $\delta$ -N-nitroguanylggramicidin S was converted into Ph-amino- $\delta$ -N-guanylggramicidin S. This derivative contained two guanidine groups belonging to the arginine residues, and two aromatic amino groups of the aminophenylalanine. Like Ph-amino-gramicidin S it was easily soluble in water. It is clear in the case of these derivatives that introduction of the amino group in the phenylalanine residue is sharply reflected in the solubility of the gramicidin S.

Since we had only a very small amount of substance, we could not establish exactly how the nitro and the corresponding amino groups were placed in the aromatic ring of phenylalanine. The literature indicates that on nitration of phenylalanine the nitro group as a rule occupies the para-position [10-12]. This gives us reason to suppose that in our case in the nitration of gramicidin S and its derivatives there is substitution of the hydrogen atom in the aromatic ring of phenylalanine in the para-position to the aliphatic side chain. However, we cannot exclude the possibility of formation of the ortho-isomer.

Below we give a scheme for the preparation and reciprocal reactions of the phenyl substituted derivatives of gramicidin S.



Scheme of synthesis and transformations of phenyl-substituted derivatives of gramicidin S.

(I)-Gramicidin S; (II)-ph-nitrogramicidin S; (III)-Ph-amino-gramicidin S; (IV)-Ph-diazo derivative of gramicidin S; (V)- $\delta$ -N-nitroguanylggramicidin S; (VI)-Ph-nitro- $\delta$ -N-nitroguanylggramicidin S; (VII)-Ph-amino- $\delta$ -N-guanylggramicidin S.

The antibacterial action of Ph-substituted derivatives of gramicidin S (inhibition of growth of *Staphylococcus aureus*) was studied by A. N. Polin, to whom the authors express thanks.

Study of Ph-nitrogramicidin S showed that it did not differ in activity from the starting antibiotic. The same result was obtained by M. P. Znamenskaya and A. N. Belozerskii [2]; therefore, we can consider it firmly established that nitration in the phenylalanine residue of the gramicidin S is not reflected in its activity. The D-phenylalanine

residue cannot be considered as a strictly specific element in the structure of gramicidin S. It is important to remember that introduction of the nitro group in gramicidin S has little effect on the physicochemical properties and does not change the ratio of polar and nonpolar parts of the antibiotic molecule.

On the other hand, introduction of amino groups in the aromatic ring of phenylalanine strongly decreases the antibiotic activity of the gramicidin S. This was established by study of two derivatives: Ph-aminogramicidin S and Ph-amino- $\delta$ -N-guanyl-gramicidin S, and in both cases the value for the activity was about the same and was about 1/15 the activity of gramicidin S.

This fact is the more interesting because Ph-amino derivatives of gramicidin S have all the structural characteristics which are usually considered necessary for the antibiotic action of gramicidin S. They contain the D-amino acid, have the cyclic structure, and have free amino groups. Moreover, besides the two free  $\delta$ -amino groups of the ornithine or guanidine group of arginine, the molecules have two aromatic amino groups of the aminophenylalanine. In spite of all this, the antibiotic activity of Ph-amino derivatives is very low.

We should observe that Ph-amino derivatives of gramicidin S are easily soluble in water. Evidently, introduction of the polar amino groups in the phenylalanine residue leads to "hydrophilization" of the nonpolar part of the gramicidin S molecule. As a result, the coupling of the polar and nonpolar parts of the molecule which is characteristic for the gramicidin structure is destroyed. We can assume that this destruction also determines the lessened activity of the modified antibiotic.

#### EXPERIMENTAL

**Preparation of Ph-nitrogramicidin S (II).** We dissolved 1.08 g of gramicidin S (1.8 m-equiv.) in 4 ml of concentrated sulfuric acid. After cooling to 10°C we added at one time 1 ml of nitric acid (sp. gr. 1.42) free from oxides of nitrogen. After stirring for 5 minutes, the mixture stood for 30 minutes at room temperature. Then the solution was poured onto 20 g of ice and the resulting precipitate was filtered off and washed with water. The color of this precipitate was bright yellow. After washing with a small amount of acetone and ether, the precipitate was dried over phosphoric anhydride. We obtained 1.04 g of Ph-nitrogramicidin S sulfate (82%). The substance was apparently a mixture of acid and neutral sulfates of Ph-nitrogramicidin S and did not have a clear melting point (it decomposed at 250-260°C); it gave a ninhydrin reaction. The Yanovskii reaction for dinitro compounds was negative. For analysis the substance was converted to the free base and then into the neutral sulfate.

To a suspension of unpurified Ph-nitrogramicidin S sulfate in 15 ml of methanol we added 2 N sodium hydroxide to an alkaline reaction to phenolphthalein. Addition of a small amount of acetone dissolved the substance, after which the Ph-nitrogramicidin S was precipitated with water. After washing with water and drying at 105°C we obtained 620 mg of an orange-yellow substance which melted with decomposition at 228-230°C. To a solution of Ph-nitrogramicidin S in the minimum amount of a mixture of acetone-water-acetic acid (3:1:1) we added sulfuric acid to an acid reaction to Congo. The precipitate of Ph-nitrogramicidin S sulfate was filtered off, washed with water, acetone, and ether. We obtained 530 mg of substance which was slightly yellow.

Found %: C 52.52, 52.58; H 6.58, 6.51; N 14.16, 14.19.  $C_{60}H_{90}O_{14}N_{14} \cdot 2H_2O \cdot H_2SO_4$ . Calculated %: C 52.78; H 7.04; N 14.30.

In paper electrophoresis the substance behaved like gramicidin S.

In obtaining Ph-nitrogramicidin S we can start from the more available gramicidin S hydrochloride. When the latter is dissolved in concentrated sulfuric acid there is intense evolution of hydrogen chloride. Nitric acid can be added only after complete evolution of HCl.

**Preparation of Ph-aminogramicidin S (III).** To a solution of 4 g (5.8 m-equiv.) of Ph-nitrogramicidin S in a mixture of 20 ml of glacial acetic acid and 15 ml of methanol we added 250 mg of palladium black. Hydrogenation was carried out in a closed system with shaking at room temperature and atmospheric pressure. Absorption of hydrogen quickly slowed down and stopped completely after eight hours. A sample of the solution deposited on paper after treatment with nitrous acid and alkaline solution of  $\beta$ -naphthol gave a bright orange color (diazo reaction), which shows the presence of an aromatic amino group.

At the end of the hydrogenation the catalyst was filtered off, and washed with methanol; the filtrate was evaporated in a vacuum and a stream of carbon dioxide to small volume. The thick orange solution which remained in the flask was poured into a dilute solution of ammonia heated to 70°C. The oil which precipitated quickly solidified.

The precipitate was filtered, washed with dilute ammonia, and dried over sulfuric acid. We obtained 2.4 g of Ph-aminogramicidin S. The substance was a powder, soluble in water and weak acid solutions, insoluble in alkaline solutions.

TABLE 1. Paper Electrophoresis of Gramicidin S and Ph-Aminogramicidin S. (Electrolyte 30% acetic acid; length of paper strip 34 cm, voltage 220 v, length of electrophoresis 9 hours)

Name of substance	Method of developing	Distance of observed spot from point of origin (shift to cathode, cm).
Gramicidin S	Ninhydrin	10
Ph-Aminogramicidin S	Ninhydrin	11.5
	Nitrous acid + $\beta$ -naphthol	11.5

**Ph-aminogramicidin S picrate.** Six hundred mg of Ph-aminogramicidin S was dissolved in a mixture of 10 ml of water, 5 ml of methanol, and 3 ml of n-propyl alcohol. To the hot solution was added 550 mg of picric acid dissolved in a mixture of propanol-methanol (1:1). After cooling, the precipitate of picrate was filtered off. We obtained 1 g of orange-yellow substance with m.p. 186-188°C (decomposition).

Found%: C 47.77, 47.79; H 5.67, 5.73.  $C_{60}H_{94}O_{10}N_{14} \cdot 2H_2O \cdot 4C_6H_3O_7N_3$ . Calculated %: C 47.53; H 5.22.

**Qualitative amino acid composition of Ph-aminogramicidin S.** Ph-aminogramicidin S was hydrolyzed with 6 N HCl at 110°C for 35 hours. The amino acid composition of the hydrolyzate was determined by two dimensional paper chromatography. As solvents we used the following mixtures: No. 1, methanol-water-pyridine (20:5:1), and No. 2, butanol-water-diethylamine (10:5:1). Identification of the amino acids of the hydrolyzate gave the following results (Table 2).

TABLE 2. Paper Chromatography of the Hydrolyzate from Ph-aminogramicidin S

Amino acid	$R_f$ value	
	Solvent No. 1	Solvent No. 2
Ornithine. . . . .	0.09-0.32	0.22
Proline . . . . .	0.53	0.35
Valine. . . . .	0.59	0.41
Leucine . . . . .	0.60	0.51
Aminophenylalanine . . . . .	0.41	0.38

The spot corresponding to aminophenylalanine gave a positive diazo reaction. The spot of phenylalanine, which is well shown in two dimensional chromatography of the hydrolyzate from gramicidin S ( $R_f$  in solvent No. 1 0.45-0.55 and in solvent No. 2, 0.50-0.57), was absent in this case.

**Deamination of Ph-aminogramicidin S.** To a solution of 600 mg (0.6 m-equiv.) of Ph-aminogramicidin S picrate in 5 ml of glacial acetic acid was added 5 ml of 2 N hydrochloric acid and 20 ml of water. The picric acid was extracted with ether (5 x 10 ml). The solution of Ph-aminogramicidin S, freed from picric acid, was cooled to 1°C, then with stirring and cooling with ice, 40 mg (0.58 mmole) of sodium nitrite in 1 ml of water was added to it. The acidity of the solution (to Congo red) was controlled during the reaction, as was the presence of unreacted nitrite (iodine-starch paper) and the formation of a diazo compound. Twenty minutes after addition of sodium nitrite to the mixture which contained diazo compound (IV) we added a solution of hypophosphorous acid obtained by passing a solution of 1 g of calcium hypophosphite through a column with sulfopolystyrene cationite KU-2 in the  $H^+$  form (150 x 10 mm). Since no evolution of nitrogen here occurred we added to the mixture in the course of one hour another 4 g of calcium hypophosphite.

Slow evolution of gas bubbles began. After keeping for 15 hours at 5° the mixture ceased to give a diazo reaction. The precipitate (600 mg) was washed and dried over phosphoric anhydride. For purification it was recrystallized from a mixture of ethyl alcohol and 1 N HCl. We obtained 320 mg of crystalline substance with m.p. 285-288° (decomposition). On paper electrophoresis the substance behaved in the same way as gramicidin S.

Preparation of Ph-nitro- $\delta$ -N-nitroguanyl-gramicidin S (VI). We dissolved 412 mg (0.63 m-equiv.) of  $\delta$ -N-nitroguanyl-gramicidin S [3] at room temperature in 3 ml of concentrated sulfuric acid. We added 0.2 ml of nitric acid (sp. gr. 1.5) which did not contain oxides of nitrogen. After 30 minutes the mixture was poured onto 60 g of ice. The resulting precipitate was washed with hot water and dried at 105°C (during washing the precipitate took on a yellow color). After recrystallization from a mixture of anhydrous formic acid and acetone, we obtained 333 mg of light yellow, strongly electrifiable powder. Yield 75%. The substance melted with violent decomposition and evolution of gas at 268-270°C. Ph-nitro- $\delta$ -N-nitroguanyl-gramicidin S was not soluble in water, alcohol, acetone, acetic acid, ether, ethyl acetate, dioxane or pyridine. Easily soluble in anhydrous formic acid.

Found %: C 51.88, 51.67; H 6.71, 6.72; N 19.02, 19.07.  $C_{65}H_{92}O_{18}N_{20} \cdot 2H_2O$ . Calculated %: C 51.64; H 6.71; N 19.44.

Because of the insolubility of the substance in water, we could not study its paper electrophoresis.

Preparation of Ph-amino- $\delta$ -N-guanyl-gramicidin S (VII). To a solution of 600 mg (0.83 m-equiv.) of Ph-nitro- $\delta$ -N-nitroguanylgramicidin S in a mixture of 8 ml of formic acid, 1 ml of water, and 0.5 ml of concentrated hydrochloric acid was added 100 mg of palladium catalyst. The resulting solution was shaken in a stream of hydrogen for 24 hours. The catalyst was removed by filtration, the filtrate was evaporated dry in a vacuum in a stream of carbon dioxide. The residue was heated for 10 minutes with 1 N hydrogen chloride in methanol. After distillation of the methanol in a vacuum the residue was dissolved in 5 ml of water and treated with a solution of 700 mg of picric acid in 50 ml of hot water. An oil precipitated which solidified immediately on cooling (873 mg). After reprecipitation by water from alcohol we obtained 676 mg of powdery substance with an orange-yellow color. Yield 72 %, m.p. 174-176°C (decomposition).

Found %: C 46.92, 46.75, H 5.48, 5.49; N 18.56, 18.40.  $C_{62}H_{90}O_{17}N_{18} \cdot 2H_2O \cdot 4C_6H_3O_7N_3$ . Calculated %: C 46.78; H 5.20; N 19.03.

TABLE 3. Paper Electrophoresis of Guanyl-gramicidin S and Ph-amino-S-N-guanyl-gramicidin S. (Electrolyte 30% acetic acid, length of paper strip 34 cm, voltage 220 v, length of electrolysis seven hours )

Substance deposited	Process of development	Distance of spot from deposition point (shift to cathode in cm)
$\delta$ -N-Guanyl-gramicidin S	Sakaguchi reaction	6.5
Ph-amino- $\delta$ -N-guanyl-gramicidin S	Sakaguchi reaction	9.2
	Nitrous acid + $\beta$ -naphthol	9.2

When hydrogenation was carried out in the absence of hydrochloric acid we did not obtain an electrophoretically homogeneous product of the reaction since the resulting aromatic amino group was partly formylated.

Microbiological studies were made with Ph-amino- $\delta$ -N-guanylgramicidin S and Ph-aminogramicidin S isolated from the corresponding picrates using anionite EDE-10 in the OH' form.

#### SUMMARY

1. We have synthesized the following Ph-substituted derivatives of gramicidin S: Ph-nitrogramicidin S, Ph-nitro- $\delta$ -N-nitroguanylgramicidin S, Ph-aminogramicidin S, Ph-amino- $\delta$ -N-guanyl-gramicidin S.

2. We have shown that the introduction of the nitro group in the gramicidin S molecule does not change the antibacterial action of the antibiotic, while introduction of an aromatic amino group in the phenylalanine residue lowers the activity.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.

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# THE PREPARATION OF DERIVATIVES OF GRAMICIDIN S WHICH CONTAIN CARBOXYL GROUPS

V. M. Stepanov and A. B. Silaev

M. V. Lomonosov Moscow State University

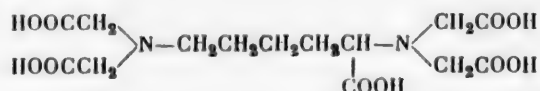
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A characteristic peculiarity of the chemical structure of the antibiotic-polypeptide gramicidin S is that the only free functional group in its molecule is an amino group. It is interesting that not only in the molecule of gramicidin S, but also in the molecule of the related antibiotics gramicidin J and tyrocidine there are no free carboxyl groups. It is evident that the introduction into the molecule of gramicidin S of even one carboxyl group should produce amphoteric properties. It is natural to assume that such a change in the chemical nature of the antibiotic would be reflected in the biological activity. All this makes it interesting to prepare derivatives of gramicidin S which would contain one or more free carboxyl groups.

In 1956 a simple method was suggested for introducing carboxymethyl groups into molecules of amino acids, peptides, and proteins [1,2]. At pH 9 these compounds easily react with the anion of bromoacetic acid and all the hydrogen atoms of the amino groups are replaced stepwise by carboxymethyl groups. For example, tetracarboxymethyllysine can be prepared from lysine.



The authors report that the nitrogens of the amino groups which undergo carboxymethylation retain basic properties.

We have carried out carboxymethylation of gramicidin S by treating a solution of the antibiotic in dioxane with excess bromoacetic acid in the presence of potash at 40°C. Under these conditions there is complete replacement of the hydrogen atoms of both amino groups of gramicidin S and δ-N,N'-tetracarboxymethyl-gramicidin S is formed with a yield of 69%. This derivative of gramicidin S contains two tertiary amino and four carboxyl groups.

It was especially interesting to prepare such a derivative of gramicidin S in which the basic properties would predominate over the acidic. Since selective carboxymethylation of only one amino group of gramicidin S could not be carried out, we decided to run a partial carboxymethylation of gramicidin S and to isolate from the mixture of reaction products monocarboxymethyl-gramicidin S. For this purpose, gramicidin S was reacted with an amount of bromoacetic acid known to be insufficient. Per 1 mole of gramicidin S (calculated on the decapeptide with two amino groups) we took 0.5 mole of bromoacetic acid.

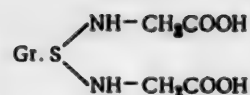
Theoretically, the mixture of products of partial carboxymethylation of gramicidin S can contain the following components.

- |   |       |   |
|---|-------|---|
| 1) Unreacted gramicidin S .....         | Gr. S | $\begin{array}{l} \text{NH}_2^+ \\ \text{NH}_2 \end{array}$             |
| 2) Monocarboxymethyl-gramicidin S ..... | Gr. S | $\begin{array}{l} \text{NH-CH}_2\text{COOH} \\ \text{NH}_2 \end{array}$ |

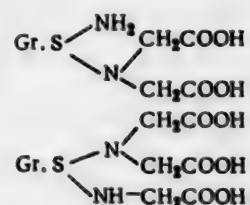
\* Here and later Gr. S is an abbreviation denoting all the molecule of gramicidin S except the free amino groups of ornithine.



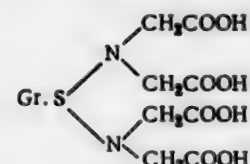
- 3) Dicarboxymethyl-gramicidin S (two isomers are possible,  
not separated by electrophoresis)



- 4) Tricarboxymethyl-gramicidin S .....



- 5) Tetracarboxymethyl-gramicidin S .....



The introduction into the gramicidin S molecule of each carboxyl group causes a specific decrease in the rate at which the substance moves to the cathode in paper electrophoresis. Therefore it is possible to carry out an electrophoretic analysis of the complex mixture of products from incomplete carboxymethylation of gramicidin S. We observed four zones on the electrophoretogram. The zone which moved most rapidly to the cathode was gramicidin S. The zone which followed it contained monocarboxymethyl-gramicidin S, the third zone probably was the disubstituted derivative. Under our conditions, separation of the tri- and tetracarboxymethyl-gramicidin S did not occur.

For separation of monocarboxymethyl-gramicidin S from the reaction mixture we used the method of preparative electrophoresis on cellulose powder. As a result of a very laborious purification, we succeeded in obtaining  $\delta$ -N-monocarboxymethyl-gramicidin S which contained a slight admixture of the disubstituted derivative and was entirely free from gramicidin S. This derivative contained one carboxyl and two amine groups.

Determination of the antibacterial activity of the resulting derivatives was carried out by A. N. Polin to whom the authors express thanks. It was shown that under those conditions in which gramicidin S inhibited the growth of *Staphylococcus aureus* at a concentration of  $1.5 \mu\text{g/ml}$  the tetracarboxymethyl-gramicidin S showed no action even at  $100 \mu\text{g/ml}$ . Monocarboxymethyl-gramicidin S hindered the growth of *Staphylococcus aureus* at a concentration of  $23 \mu\text{g/ml}$ . Thus introduction of even one carboxyl group in the molecule of gramicidin S leads to a sharp decrease in antibacterial activity.

The effect of the carboxyl group in the biological activity as shown by study of the carboxymethyl derivatives of gramicidin S is important to consider in estimation of the activity of compounds which are models for the structure of gramicidin S. Erlanger and co-worker [3] showed that linear synthetic decapeptides with the same sequence of amino acids as in gramicidin S acted 12-40 times more weakly on bacteria than did the cyclodecapeptide. However, the linear peptide as distinguished from the cyclopeptide has a carboxyl group, and therefore its activity is more correctly comparable to the activity of the monocarboxymethylgramicidin S which is about 1/15 the activity of gramicidin S. As can be seen, the order of magnitude in both cases is the same.

The results of the study of carboxymethylation of gramicidin S show that the absence of a carboxyl group in the molecule of gramicidin S, gramicidin J, and tyrocidine cannot be considered chance. This characteristic peculiarity of structure of the antibiotic group of gramicidin S is firmly connected with their biological activity.

#### EXPERIMENTAL

**$\delta$ -N,N'-Tetracarboxymethyl-gramicidin S.** To a solution of 400 mg (0.64 m-equiv.) of gramicidin S hydrochloride in 15 ml of dioxane and 10 ml of water was added 1.38 g (10 mmole) of potassium carbonate and 1 g (7.1 mmole) of bromoacetic acid. The mixture was kept in a thermostat for 12 hours at  $40^\circ$ . For separation of the reaction product, the solution was acidified to Congo red with hydrochloric acid and the resulting small precipitate was filtered off; the filtrate was poured into three times its volume of hot water. The precipitate which formed after keeping it for 12 hours in a refrigerator was filtered off, washed with a small amount of water, and dried at  $90^\circ\text{C}$ .

We obtained 316 mg of a white, powdery substance. Yield 69%. M. p. 258-260°C. After reprecipitation by petroleum ether from absolute methylene chloride we obtained 240 mg of substance with m.p. 259-261°C.

Found %: C 57.78; 57.59; H 7.62; 7.59; N 11.84, 11.78.  $C_{22}H_{20}O_{12}N_{12} \cdot 2H_2O$ . Calculated %: C 57.94; H 7.44; N 11.92.

The substance did not give a ninhydrin reaction and on paper electrophoresis in 30% acetic acid it remained at the point of deposition.

**Monocarboxymethyl-gramicidin S.** To a solution of 960 mg (1.65 m-equiv.) of gramicidin S and 280 mg (4 m-equiv.) of potassium carbonate in 20 ml of dioxane and 5 ml of water we added 1 ml of 1 N solution of bromoacetic acid in dioxane. The mixture was kept in a thermostat at 40°C. After 48 hours we added to it hot 1 N hydrochloric acid to the appearance of a precipitate. After cooling, the precipitate was filtered off, washed with dilute alcohol, and dried at 110°C. We obtained 780 mg of a white, crystalline substance.

Paper Electrophoresis of the Products of Partial Carboxymethylation of Gramicidin S.  
(Electrolyte 30% acetic acid, length of paper strip 34 cm, voltage 220 v, duration 4.5 hours)

Deposited Substance	Method of development	Distance of observed spot from point of deposition (shift to cathode in cm)
Gramicidin S	Ninhydrin	4.3
	Solution of iodine in methanol	4.3
Tetracarboxymethyl-gramicidin S	Solution of iodine in methanol	0
Mixture of products of partial carboxymethylation	Ninhydrin	4.2, 3.0, 1.5 (weak)
	Solution of iodine in methanol	4.2, 3.0, 1.5 (weak) 0

The mixture of products of partial carboxymethylation was separated by preparative electrophoresis on cellulose powder.

For the separation 250 mg of mixture we used a moist layer of cellulose powder 300 mm long, 65 mm wide, and 6 mm high. We used 30% acetic acid as the electrolyte. After electrophoresis, which lasted for ten hours at 220 v and current strength 20 mA, a strip of chromatographic paper was laid on the layer of cellulose powder. After one minute it was removed, dried, and developed with a solution of iodine in methanol and with ninhydrin. We noted the following zones shifting toward the cathode, on this "print:"

- 1) 9-12 cm from the starting line (clear band, developed by ninhydrin and iodine);
- 2) 6-8 cm from starting line (clear band, developed by ninhydrin and iodine);
- 3) 2-5 cm from starting line (weakly developed by ninydrin, somewhat more clearly by iodine);
- 4) a zone at the starting line, width 1 cm (developed only by iodine).

Part of the moist layer corresponding to the second zone was removed from the cuvette and transferred to a glass filter. The electrolyte was filtered off and the powder which remained on the filter was washed with 100 ml of methanol; the resulting solution was evaporated dry in a vacuum. In three cases we separated 750 mg of mixture and we isolated 320 mg of unpurified monocarboxymethyl derivative of gramicidin S. For further purification, the substance was submitted once more to preparative electrophoresis under the same conditions, which permitted us to free the mixture from gramicidin S. After reprecipitation by petroleum ether from absolute acetone we obtained 140 mg of the acetate of  $\delta$ -N, monocarboxymethylgramicidin S. M. p. 236-239°C.

Found %: C 57.97; 57.87; H 7.97, 7.99.  $C_{22}H_{20}O_{12}N_{12} \cdot CH_3COOH \cdot 2H_2O$ . Calculated %: C 59.35; H 8.02.

On paper electrophoresis under conditions analogous to those described above we obtained a substance after four hours which moved 3.0 cm to the cathode. Gramicidin S in this time moved 4.1 cm.

#### SUMMARY

1. We have obtained tetracarboxymethyl-gramicidin S and monocarboxymethyl-gramicidin S.
2. We have shown that introduction of the carboxyl group in the gramicidin S molecule leads to a sharp fall in antibiotic activity.

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## THE STRUCTURE OF THE ALKALOID RENARDINE. II. \*

A. V. Danilova, N. I. Koretskaya, and L. M. Utkin

S. Ordzhonikidze All-Union Research Chemicopharmaceutical Institute

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As a result of a careful study of the properties of the alkaloid renardine, isolated from *Senecio renardi* C. Winkl., we have shown that its composition corresponds to the formula  $C_{19}H_{27}O_6N$ , and not  $C_{18}H_{25}O_6N$  as was reported previously [1]. Since we could not use the method of alkaline hydrolysis for the preparation of necine, because of formation of tarry products, we were left with the choice of the method of hydrolysis of renardine by hydrochloric acid and the method of hydrogenolysis. On hydrolysis of renardine by aqueous hydrochloric acid we obtained the lactone of senecinic acid and a mixture of substances with a basic character. By chromatography of the mixture on cellulose we isolated two individual substances as hydrochlorides. One of them had the composition  $C_9H_{15}O_3N \cdot HCl$  and in its infrared spectrum showed absorption bands characteristic of the hydroxyl group. From the melting point and empirical formula it was identical with the hydrochloride of othonecine obtained by E. S. Zhdanovich and G. P. Men'shikov [2]. The second hydrochloride had the composition  $C_9H_{13}O_3N \cdot HCl$  and we called it anhydroothonecine hydrochloride.

In the hydrogenolysis of renardine in hydrochloric acid with Pt from  $PtO_2$  we obtained dihydrosenecinic acid and hydronecine with the composition  $C_9H_{17}O_2N$ .

Dihydrosenecinic acid and the lactone of dihydrosenecinic acid have not been characterized in the literature [3] with sufficient fullness. We have determined their constants and obtained the previously undescribed dimethyl ester of dihydrosenecinic acid.

For comparison of the properties of the triols obtained earlier from the acids which occur in the composition of platyphilline and neoplatyphilline [4] with the properties of dihydrosenecinetriol, we carried out reduction with lithium aluminum hydride of the dimethyl ester of dihydrosenecinic acid. The resulting triol was a gummy substance which formed a crystalline p-nitrobenzoyl derivative.

In comparing the properties of hydronecine and its salts with the properties of hydroothonecine which we obtained by hydrogenolysis of the alkaloid othosenine, we established their identity. Hydroothonecine was previously obtained by E. S. Zhdanovich and G. P. Men'shikov [2] by reduction according to Adams of othonecine hydrochloride. Hence, renardine and othosenine differ only in the esterified acids.

In studying the properties of renardine, othosenine, othonecine, and hydroothonecine, we established that they reduce an ammoniacal silver hydroxide solution with formation of a silver mirror, but at the same time they do not give the usual derivatives characteristic of aldehydes and ketones. The infrared spectra of othonecine and hydroothonecine have absorption bands characteristic for the hydroxyl group and do not contain the bands of the carbonyl group. However, E. S. Zhdanovich and G. P. Men'shikov [2] obtained an oxime of hydroothonecine by carrying out the reaction in a strongly alkaline medium and concluded on this basis that a carbonyl group was present in othosenine. When we tried to form an oxime from hydroothonecine under the same conditions, we succeeded in isolating two isomeric substances. One of them was identical with the oxime obtained by E. S. Zhdanovich and G. P. Men'shikov and had the composition  $C_9H_{18}O_2N_2$ . From the mother liquor from recrystallization of this oxime we isolated a second substance of the same composition, but differing in its physicochemical properties and infrared spectrum.

Starting from the above facts, we consider it most probable that the carbonyl function arises during the reaction because of a tautomeric transformation in the molecule of hydroothonecine.

\* For communication I, see [1].

## EXPERIMENTAL \*

Renardine. The base was isolated from the bitartrate and was recrystallized from alcohol. M.p. 193-194°C,  $[\alpha]_D^{20} 0 \pm 2^\circ$  (CHCl<sub>3</sub>).

Found %: C 62.48; H 7.44; N 3.94; NCH<sub>3</sub> 8.13, Equiv. 365.25. C<sub>19</sub>H<sub>27</sub>O<sub>6</sub>N. Calculated %: C 62.45; H 7.45; N 3.83; NCH<sub>3</sub> 7.95. Equiv. 365.38.

The bitartrate was precipitated by the action of tartaric acid on the technical mixture of alkaloids of Senecio renardi C Winkl. in alcohol solution (the bitartrates of the accompanying alkaloids othosenine and seneciphylline remained in the mother liquor). M.p. 197-197.5°C (from alcohol or acetone),  $[\alpha]_D^{20} -13^\circ$  (c 10.0, water).

Found %: C 53.24; H 6.41; N 2.87. C<sub>19</sub>H<sub>27</sub>O<sub>6</sub>N · C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>. Calculated %: C 53.58; H 6.45; N 2.72.

Hydrolysis of renardine by hydrochloric acid. We boiled 5.6 g of renardine in 40 ml of 15% hydrochloric acid for ten hours. The acid solution was extracted with ether and gave 2.7 g of substance identified as the lactone of senecinic acid. The water solution after removal of the lactone was evaporated in a vacuum, the residue was dissolved in 40 ml of butanol saturated with 5% HCl, and passed through a column with 370 g of cellulose powder. It was eluted with the same solution. We collected fractions of 130 ml (after the eluate gave a positive reaction for alkaloids). From fractions 7-10 we isolated 0.43 g of crystalline anhydroothonecine hydrochloride. M.p. 203-205° (from anhydrous alcohol, Koffler block),  $[\alpha]_D^{20} 0 \pm 2^\circ$  (c 1.7, alcohol).

Found %: C 52.89; H 6.76; N 7.02; Cl 17.22. C<sub>9</sub>H<sub>13</sub>O<sub>2</sub>N · HCl. Calculated %: C 53.07; H 6.93; N 6.88; Cl 7.41.

From fractions 12-19 we obtained 0.40 g of crystals of othonecine hydrochloride with m.p. 143°C (from anhydrous alcohol).

Found %: N 6.47; Cl 15.80. C<sub>9</sub>H<sub>15</sub>O<sub>3</sub>N · HCl. Calculated %: N 6.32; Cl 15.99.

Hydrogenolysis of renardine. Three g of renardine in 10 ml of 1 N HCl was reduced with Pt from 0.3 g of PtO<sub>2</sub>. There was absorption of 3.5 moles of hydrogen. The solution was evaporated in a vacuum at 45-50°C to a volume of 2 ml, made alkaline with 3 ml of 25% ammonia, and extracted with chloroform; then 2 ml of 40% sodium hydroxide was added and hydroothonecine was exhaustively extracted with chloroform. From the combined chloroform extracts we obtained 1.57 g of hydroothonecine in the form of a mobile liquid with a greenish yellow color which darkened rapidly on standing. B.p. 72-74°C at 8 mm,  $[\alpha]_D^{20} -18.17^\circ$  (c 4.51, CH<sub>3</sub>OH).

Found %: C 63.44; H 9.97; N 8.45. C<sub>9</sub>H<sub>17</sub>O<sub>2</sub>N. Calculated %: C 63.13; H 10.01; N 8.18.

The bitartrate of hydroothonecine was obtained by boiling an alcohol solution of hydroothonecine with an equimolecular amount of tartaric acid. M.p. 171-173°C (from alcohol),  $[\alpha]_D^{20} 0 \pm 2^\circ$  (c 6.1, water).

Found %: C 48.63; H 7.17; N 4.23. C<sub>9</sub>H<sub>17</sub>O<sub>2</sub>N · C<sub>4</sub>H<sub>6</sub>O<sub>6</sub>. Calculated %: C 48.59; H 7.21; N 4.36.

There was no depression of melting point when this was mixed with hydroothonecine bitartrate obtained in the hydrogenolysis of othosenine.

Hydrochloride. M. p. 240-242°C (from anhydrous alcohol, Koffler block),  $[\alpha]_D^{18} -30.40^\circ$  (c 5.07, alcohol).

Found %: Cl 16.95. C<sub>9</sub>H<sub>17</sub>O<sub>2</sub>N · HCl. Calculated %: Cl 17.11.

Hydriodide. M. p. 159-161°C (with decomposition, from alcohol),  $[\alpha]_D^{20} 19.1^\circ$  (c 2.94, anhydrous alcohol).

Found %: N 4.45. C<sub>9</sub>H<sub>17</sub>O<sub>2</sub>N · HI. Calculated %: N 4.68.

Oximes. We boiled 4.75 g of hydroothonecine in 40 ml of alcohol and 4.0 g of hydroxylamine hydrochloride in 20 ml of 40% NaOH for two hours and 40 minutes. The solution was evaporated to half volume in a vacuum, acidified with HCl, again evaporated in a vacuum to a volume of 10 ml, made alkaline with ammonia in the presence of ether, and exhaustively extracted with ether. We isolated 1.74 g of substance with m.p. 128-130°C. After recrystallization from acetone we obtained 0.65 g of the first oxime with m.p. 181.5-183°C and  $[\alpha]_D^{20} +68.8^\circ$  (c 3.3, alcohol). The oxime gave no melting point depression when mixed with the oxime obtained by E. S. Zhdanovich and G. P. Men'shikov. The picrolonate formed by mixing alcoholic solutions of the oxime and picronic acid. M.p. 133-135°C (from alcohol).

\* The analyses were carried out in the Microanalysis Laboratory of our Institute. The infrared spectra were taken in the Physical Chemistry Laboratory under the direction of Yu. N. Sheinker.

Found %: N 17.72.  $C_9H_{11}O_2N_2 \cdot C_{10}H_9O_2N_4 \cdot H_2O$ . Calculated %: N 17.94.

The mother liquor from the recrystallization of the first oxime yielded the second oxime. Weight 0.6 g, m.p. 131.5-133°C (from benzene),  $[\alpha]_D^{20} + 90.8^\circ$  (c 3.3, alcohol).

Found %: C 58.23; H 9.65; N 15.09.  $C_9H_{11}O_2N_2$ . Calculated %: C 58.03; H 9.74; N 15.04.

The picrolonate of the second oxime did not precipitate from alcohol solution.

**Dihydroscenecinic acid.** The alkaline solution after removal of the hydroothonecine was acidified with 20%  $H_2SO_4$  and extracted with ether. After distillation of the ether and drying of the residue in a vacuum desiccator we obtained 1.3 g of dihydroscenecinic acid in the form of a thick oil.  $[\alpha]_D^{20} + 19.96^\circ$  (c 3.0, alcohol).

Found %: C 54.91; H 8.26.  $C_{10}H_{11}O_5$ . Calculated %: C 55.03; H 8.31.

**Lactone.** Dihydroscenecinic acid (3.1 g) in 20 ml of 20%  $H_2SO_4$  was boiled for two hours. The acid solution was extracted with ether and we obtained 2.57 g of oily residue which crystallized after vacuum distillation at 185-190°C (5 mm). M.p. 121-123°C (from a mixture of benzene and petroleum ether, 1:2),  $[\alpha]_D^{20} - 19.63^\circ$  (c 8.76, alcohol).

Found %: C 60.01; H 8.03.  $C_{10}H_{16}O_4$ . Calculated %: C 59.98; H 8.05.

**Dimethyl ester of dihydroscenecinic acid.** We allowed 3.5 g of dihydroscenecinic acid in an ether solution of diazomethane (from 8 g of nitrosomethylurea) to stand for 48 hours at 20°C. We obtained 4.0 g of the dimethyl ester in the form of a clear, colorless liquid. B.p. 149-150°C (3 mm),  $d_4^{20} 1.068$ ;  $[a]_D^{20} + 7.77^\circ$  (without a solvent).

Found %: C 58.84; H 8.93.  $C_{12}H_{22}O_5$ . Calculated %: C 58.52; H 9.00.

**Reduction of the dimethyl ester by lithium aluminum hydride (dihydroscenecinetriol).** The dimethyl ester (2.55 g) in 250 ml of absolute ether was reduced with 3.5 g of  $LiAlH_4$ . We isolated 1.93 g of a thick, transparent liquid,  $[a]_D^{20} + 39.69^\circ$  (c 3.25,  $CHCl_3$ ).

**Di-p-nitrobenzoyl derivative.** To 1.67 g of dihydroscenecinetriol in 15 ml of pyridine we added 3 g of p-nitrobenzoyl chloride. After 24 hours (20°C) we added 50 ml of water to the reaction mixture and extracted with chloroform. We obtained 2.6 g of di-p-nitrobenzoyl derivative with m.p. 150-150.5°C (from alcohol),  $[a]_D^{20} + 37.05^\circ$  (c 3.67,  $CHCl_3$ ).

Found %: C 58.92; H 5.70; N 5.62.  $C_{24}H_{28}O_9N_2$ . Calculated %: C 59.01; H 5.78; N 5.74.

#### SUMMARY

1. We have established that the alkaloids renardine and othosenine have the same necine, and differ in the esterified acid.
2. We have obtained and characterized anhydroothonecine, hydroothonecine, and dihydroscenecinic acid.

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ALLOIMPERATORIN (PRANGENIDINE) - COMPONENT OF THE RESIN  
FROM THE ROOTS OF *Prangos pabularia* Lindl.

G. A. Kuznetsova

Botanical Institute, Academy of Sciences of the USSR

Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 11,

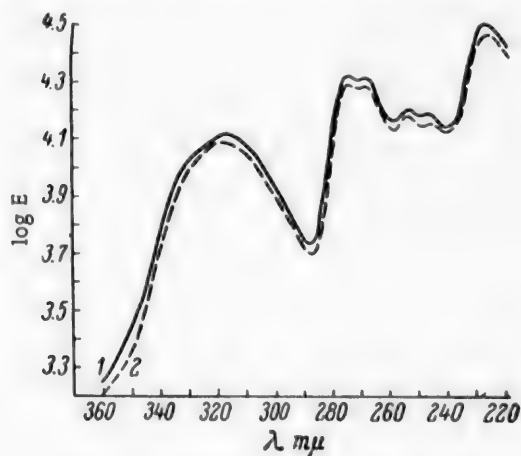
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Original article submitted October 3, 1960

In a series of papers we reported that the resin from the roots of *Prangos pabularia* Lindl. contained the coumarin and furocoumarin derivatives: *Osthole* [1], *oxypeucedanin* [1, 2], *imperatorin* [3], *prangenine* (oxide of *imperatorin* [3, 4] and a substance with m.p. 228-229°C, named *prangenidine*. On the basis of the analysis data we assigned this compound the molecular formula  $C_{16}H_{14}O_4$  and postulated [2] that it is identical with *alloimperatorin* (m.p. 233°C).

Resuming a study of the composition of the resin from the roots of *P. pabularia*, we separated the isolated mixture of furocoumarins into its components by chromatographing on aluminum oxide. From the first fraction we eluted a yellow substance (I), which after 3 recrystallizations from a mixture of chloroform and petroleum and then from alcohol had m.p. 233°C (decompn.), which supported our theory that this substance is identical with *alloimperatorin* [5, 6].

For more conclusive proof, we prepared *alloimperatorin*, with m.p. 228.5-229°C, by heating (vacuum-distillation at 2 mm) the *imperatorin* isolated from the same resin. The mixed melting point of this *alloimperatorin* and the compound with m.p. 233°C was not depressed.



Ultraviolet absorption spectra. 1) Substance (I) with m.p. 233°C; 2) *alloimperatorin*.

The ultraviolet spectra of these two compounds prove to be completely identical both as regards the positions of the maxima of the absorption bands and the intensities (see figure). Thus, for compound (I) with m.p. 233°C the maxima are found at: 318, 272, 266, 252, 244 and 222-224 mμ, while for *alloimperatorin* they are located at 316, 272, 266, 252, 244 and 222-224 mμ.

Both substances behave in the same manner when chromatographed; they give spots that are identical in both luminescence and location.

Consequently, the substance with m.p. 233°C (*prangenidine*) is identical with *alloimperatorin*.

#### EXPERIMENTAL

**Isolation of substance with m.p. 233°C.** Seven hundred grams of the resin, obtained from the alcohol extraction of *P. pabularia*, was covered with 3 liters of 10 % alcoholic NaOH solution. After 24 hr the solution was diluted with water (2 liters) and extracted with ether (to re-

move inert materials). Then the solution was made acid and subjected to exhaustive extraction with ether. The combined ether extracts were washed with water and dried over anhydrous sodium sulfate. Then the solution was filtered, and the ether was removed by distillation. The obtained mixture of furocoumarins (185 g) was passed through a column filled with  $Al_2O_3$  (500 g, 3rd activity). A mixture of chloroform and petroleum ether (1:5) was used for the elution, taking 100-ml fractions. From the first three fractions we isolated 3.95 g of substance with m.p. 215°C. After 3 recrystallizations from a mixture of chloroform and petroleum ether, and then from alcohol,

we obtained faintly yellow crystals with m.p. 233°C.

Found %: C 71.01, 71.13; H 5.17, 5.18. M 290.  $C_{16}H_{14}O_4$ . Calculated %: C 71.11; H 5.18. M 270.

On the paper chromatogram the substance gives a spot with a bright yellow luminescence in ultraviolet light around the point of deposition. The paper chromatogram was obtained by the descending technique in a pyridine atmosphere; ethylene glycol was the stationary phase, and benzine was the moving phase [3, 7].

Isomerization of imperatorin to alloimperatorin. The vacuum-distillation (at 2 mm) of 0.18 g of imperatorin gave a faintly yellow distillate. The material was recrystallized from alcohol to give alloimperatorin with m.p. 228.5-229°C. The mixed melting point of this alloimperatorin and the substance with m.p. 233°C was not depressed. The location of the spots on the paper chromatogram is the same for both compounds and is characterized by a bright yellow luminescence around the point of deposition when illuminated with ultraviolet light.

#### SUMMARY

Prangenidine (m.p. 233°C) was shown chemically, chromatographically and spectrographically to be the same as alloimperatorin.

It was found that the secretion from Prangos pabularia Lindl. contains besides the previously described oxy-peucedanin, osthole, prangenine and imperatorin, also alloimperatorin.

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# STUDY OF THE CHEMICAL STRUCTURE OF THE ANTIBIOTIC ALBOMYCIN

## I ISOLATION AND IDENTIFICATION OF THE PYRIMIDINE BASE

N. A. Poddubnaya, G. I. Lavrenova, E. P. Krysin,  
and L. G. Makevnina

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A study of the chemical structure of the iron-containing antibiotic albomycin, discovered by G. F. Gauze and M. G. Brazhnikova [1] in 1949 and isolated by them in 1951 from a culture of *Actinomyces subtropicus*, is of definite interest. The antibiotic contains in its composition a pyrimidine base, a peptide, built from several amino acids (serine, ornithine, glutamic acid), and, possibly, a carbohydrate (of as yet unknown structure). Albomycin is a metal complex containing trivalent iron, which represents a very active functional group in it, easily removed from the molecule with a loss in the activity [2]. The manner in which the iron is linked to the organic portion of the molecule still remains unanswered.

At the present time very little is known concerning the chemical nature and structure of albomycin. Several investigators have made a study of methods of purification, homogeneity, physico-chemical properties, biological activity, and the specificity of the iron entering into the composition of albomycin [2, 3].

TABLE 1. Comparison of Properties of N-methyluracils of Different Origin

Name of compound	Source	M.p.	Reaction with p-diazobenzene-sulfonic acid	Value of R <sub>f</sub> when chromatographed on paper			λ <sub>max</sub> in the ultra-violet spectrum (in mμ)	
				System No. 1	System No. 2	System No. 3	in water (pH 12)	in anhydrous ethanol
1-Methyluracil	Synthetic	174-175*	Positive	0.63	0.54	0.8	282.5	258
3-Methyluracil	Synthetic	232	Negative	0.45	0.3	0.67	262.5	265
X-Methyluracil	From albomycin	170-172	Positive	0.63	0.5	0.79	282	260
3-Methyluracil	From grisein [6]	182-183	Positive	—	—	—	278.5 (pH 7)	—

Remarks. System No. 1: Butanol-formic acid-water (77:13:10); system No. 2: aqueous Na<sub>2</sub>HPO<sub>4</sub> solution, saturated with amyl alcohol (Carter system); system No. 3: butanol-acetic acid-water (77:13:10).

The isolation of 3-methyluracil from albomycin has been reported by Sorm and Mikes [4]; in this connection they refer to the work of Kuehl [5] on the identification of the pyrimidine contained in grisein [6]. A substance was isolated from the acid hydrolysis of grisein that the authors, on the basis of the properties, identified as 3-methyluracil. However, as can be seen from a comparison with the literature data (Table 1), the N-methyluracil isolated by Kuehl is neither 3- nor 1-methyluracil (according to the nomenclature of Johnson, Heyl and Todd [7], adopted by us).

The method adopted by Kuehl to prove the structure of the isolated pyrimidine base, which consisted in identifying the products of oxidative destruction, is not conclusive, as was indicated by both Brown and Behrend [8] and was proved experimentally by us. Actually, both 1-methyluracil and 3-methyluracil can give the same products

when oxidized with potassium permanganate, and specifically,  $\omega$ -methyloxaluric and oxalic acids.

Only a synthesis of the isomeric N-methyluracils and a comparison with the material isolated from the antibiotic could give an answer to our problem.

We synthesized 1-methyluracil by the Johnson and Heyl method [9], via pseudoethylthiourea and formylacetic ester. The obtained 2-ethylmercapto-6-hydroxypyrimidine was converted by methylation to 1-methyl-2-ethylmercaptouracil which on desulfurization gave the desired compound.

The synthesis of 2-hydroxy-6-methylmercaptopyrimidine, needed for the preparation of 3-methyluracil, was accomplished through the chloro derivative of uracil [10] in which the chlorine atom is easily replaced by the thio group [11], while the methylation of 6-thiouracil leads to obtaining 2-hydroxy-6-methylmercaptopyrimidine. We did not isolate the 6-thiouracil, but instead methylated it under conditions where 2-oxo-3-methyl-6-methylmercaptopyrimidine was obtained immediately; desulfurization of the latter gave 3-methyluracil directly [12].

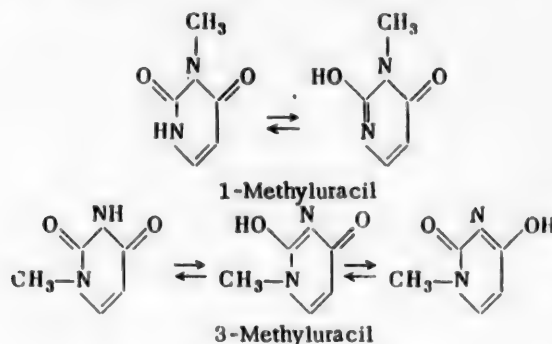
The constants of the obtained 1- and 3-methyluracils showed complete agreement with the literature data.

Since neither the chromatographing nor the electrophoresis of N-substituted pyrimidine bases has been reported in the literature, we used these methods to investigate the obtained compounds in several systems.

As can be seen from the data in Table 1, the technique of descending paper chromatography gave quite different values of  $R_f$  for the 1- and 3-methyluracils in all three systems.

These compounds behave in the same manner during electrophoresis: at low pH values they remain at the point of deposition, while at a pH greater than 7 they move at the same rate.

A difference between the two pyrimidine bases is manifested with special clarity when their ultraviolet spectra are taken at a pH of 10 to 12, where they exist in different tautomeric forms.



The ultraviolet spectra that we obtained of the two compounds at pH 12 and in anhydrous alcohol are in complete agreement with the literature data and are easily reproducible, which testifies to the purity of the 1- and 3-methyluracils (Figs. 1 and 2).

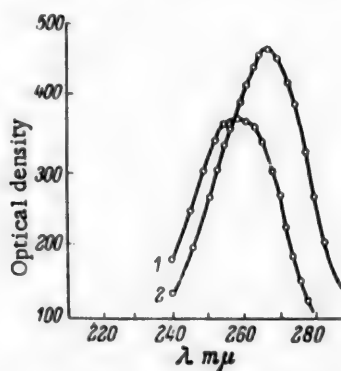


Fig. 1. Ultraviolet absorption spectra in anhydrous alcohol. 1) 1-Methyluracil; 2) 3-methyluracil.

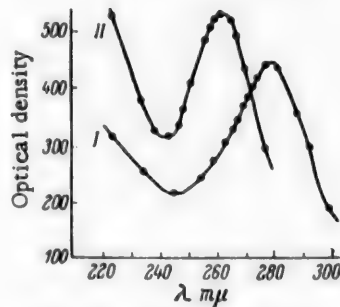


Fig. 2. Ultraviolet absorption spectra in water at pH 12. 1) 1-Methyluracil; 2) 3-methyluracil.

To isolate the pyrimidine base from the antibiotic we first separated the albomycin into 5 fractions by combining the method of chromatography with electrophoresis.

This method differs from those described in the literature, and the activity of the fractions also does not coincide with the literature data.

Electrophoresis in one direction was run in a cellulose column, in 30% acetic acid as the medium, at a voltage of 220 v, for 3 days (with cooling to 4°C). When these fractions were chromatographed in the system butanol-water-acetic acid (3:2:1) we obtained a total of 5 fractions (Fig. 3), which were tested for biological activity and whose ultraviolet absorption spectra were obtained.

Only the 2nd fraction exhibited biological activity. All of the fractions except the 4th exhibited a characteristic ultraviolet absorption spectrum at pH 7. The character of the ultraviolet absorption spectrum did not change when the iron was removed.

Albomycin, not separated into fractions, shows maximum absorption in the ultraviolet at 280 m $\mu$ , which coincides with the data of M. G. Brazhnikova and co-workers [2].

To isolate the pyrimidine base from the albomycin molecule, we hydrolyzed the material with 20% hydrochloric acid at 100°C for 24 hr. The pyrimidine base was extracted from the hydrolyzate with chloroform. The extracted base gave a positive test with p-diazobenzenesulfonic acid and had m.p. 170-172°C. The data on the chromatographing of the material are given in Table 1, while the electrophoresis data are given in Table 3; the absorption spectra of the substance in water at pH 12 and in anhydrous alcohol are shown in Fig. 4.

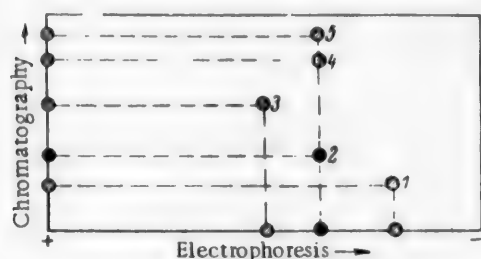


Fig. 3. Scheme for the separation of albomycin into fractions by the combined technique of chromatography and electrophoresis.

- — biologically active fraction.
- — biologically inactive fraction.

TABLE 2. Values of the Absorption Maxima in the Ultraviolet Spectra of the Individual Albomycin Fractions.

Fraction No.	$\lambda_{\text{max}}$ (in m $\mu$ )	
	Before Fe removal	After Fe removal
1	280	280
2	275	275
3	265	265
4	—	—
5	325	325

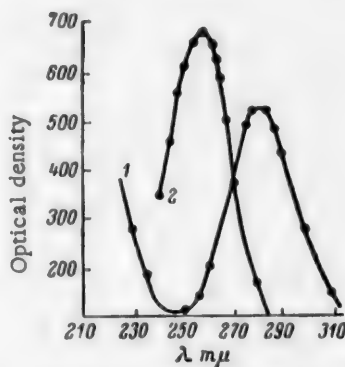


Fig. 4. Ultraviolet absorption spectra of 1-methyluracil, isolated from albomycin. 1) In 0.01 N aqueous NaOH solution (pH 12); 2) in anhydrous alcohol.

TABLE 3. Electrophoresis of X-Methyluracil, Isolated from Albomycin (at a Gradient of 4.9 v/cm)

Buffer	pH	Relative mobility (in cm)
Pyridine-acetate	5.6	0.0
30% acetic acid	3.6	0.0
Formic-acetate	1-2	0.0

As can be seen from a comparison of the data in Tables 1 and 3, and also Figs. 1, 2, and 4, all of the physicochemical constants of the isolated compound coincide exactly with the corresponding constants for 1-methyluracil, and are quite different from the constants for 3-methyluracil.

## EXPERIMENTAL

**Synthesis of 1-Methyluracil.** The ethyl ester of formylacetic acid was obtained [12] by the condensation of ethyl acetate with ethyl formate in the presence of finely comminuted sodium metal. Yield 40%.

**Pseudoethylthiourea hydrobromide** was obtained by the method given in [13]. The yield was quantitative. M. p. 86–87°C.

**2-Ethylmercapto-6-hydroxypyrimidine** was obtained by the condensation of pseudoethylthiourea with the sodium salt of ethyl formylacetate, as described in [13]. Yield 50%. M.p. 148–152°C. (Literature data [9]: m.p. 152°C).

**1-Methyl-2-ethylmercapto-6-hydroxypyrimidine** was obtained as described in [9] by the methylation of 2-ethylmercapto-6-hydroxypyrimidine with methyl iodide in 95% ethanol, in the presence of KOH. Yield 25%. M.p. 78–79°C (Literature data [9]: m.p. 79°C).

**1-Methyluracil** was obtained by refluxing 1-methyl-2-ethylmercapto-6-hydroxypyrimidine in 20% hydrochloric acid until the evolution of ethyl mercaptan ceased. Yield 90%. M.p. 172–174°C. (Literature data: M.p. 174–176°C [9]). The compound gives a red color with p-diazobenzenesulfonic acid in dilute alkali.

Found %: C 47.31, 47.46; H 5.12, 5.00; N 21.90, 21.85.  $C_5H_6O_2N_2$ . Calculated %: C 47.6; H 4.76; N 22.2. Ultraviolet absorption in aqueous alkali at pH 12:  $\lambda_{\max}$  282.5 m $\mu$  ( $\epsilon$  4200); in anhydrous alcohol:  $\lambda_{\max}$  258 m $\mu$  ( $\epsilon$  5260).

**Synthesis of 3-Methyluracil.** **2-Ethylmercapto-6-chloropyrimidine** was obtained [12] by the reaction of phosphorus pentachloride with 2-ethylmercapto-6-hydroxypyrimidine. Yield 90%.

**2-Ethylmercapto-6-thiopyrimidine** was obtained from the preceding compound by treating it for 2.5 hr with excess potassium hydrosulfide in alcohol solution. Yield 60%. M.p. 142–144°C (literature data: m.p. 149°C [12]).

**6-Thiouracil** was obtained by the treatment of 2-ethylmercapto-6-thiopyrimidine with 20% hydrochloric acid. Yield 94%. M.p. 320°C (literature data: m.p. 328°C [12]).

The yield of 6-thiouracil decreased if the refluxing with the hydrochloric acid was slightly too long, due to complete desulfurization of the 2-ethylmercapto-6-thiopyrimidine with the formation of uracil.

**2-Hydroxy-3-methyl-6-methylmercaptopyrimidine** was obtained by the methylation of 6-thiouracil with methyl iodide in sodium ethylate medium. Yield 90%. M.p. 115–120°C (Literature data: m.p. 124°C [12]).

**3-Methyluracil** was obtained by the desulfurization of 2-hydroxy-3-methyl-6-methylmercaptopyrimidine in conc. hydrochloric acid. Yield 33%. After 2 recrystallizations from water, M.p. 232°C (literature data: m.p. 232°C [12]). The qualitative test with p-diazobenzenesulfonic acid was negative.

Found %: C 47.35, 47.65; H 5.02, 4.75,  $C_5H_6O_2N_2$ . Calculated %: C 47.6; H 4.76. Ultraviolet absorption in anhydrous alcohol:  $\lambda_{\max}$  265 m $\mu$  ( $\epsilon$  4800); in aqueous alkali at pH 12:  $\lambda_{\max}$  262.5 m $\mu$  ( $\epsilon$  5260) (Figs. 1 and 2).

**Identification of Obtained Pyrimidine Bases.** **Descending chromatography.** The 1- and 3-methyluracils were chromatographed in 3 systems of solvents on Leningrad "B" paper. The obtained values are given in Table 1.

**Electrophoresis** of the 1- and 3-methyluracils was run in 4 different buffers with the pH: 1–2, 3.7, 5.6 and 12.0.

**Oxidation of 1- and 3-methyluracils.** A mixture of 10 mg of 1-methyluracil (or 3-methyluracil) and 50 mg of potassium permanganate was dissolved in 5 ml of distilled water and then allowed to stand at room temperature for 4–5 hr. The manganese dioxide was separated by centrifuging, the excess permanganate was destroyed by hydrogen peroxide, and the precipitate was washed with distilled water. The filtrate and wash waters were combined and passed through an ion-exchange column filled with KB 4- $P_2$  resin in the  $H^+$ -form. The eluate, devoid of inorganic cations, was evaporated in vacuo to dryness. A white crystalline deposit was obtained. The products from the oxidation of both pyrimidine bases had the same mobility in an electric field and the same  $R_f$  values when chromatographed in the system ethanol-water-ammonia (70:30:5.1). The main product proved to be  $\omega$ -methyloxallic acid with m.p. 187°C; oxalic acid and acetylurea (m.p. 134°C) were also found to be present.

**Study of Albomycin Hydrolyzate.** **Characterization of the material and its separation into fractions.** Albomycin is a red-brown powder, readily soluble in water, slightly soluble in methanol, and insoluble in other organic solvents. The electrophoresis of albomycin on paper in 30% acetic acid at a voltage of 220 v results in its



separation into 3 colored fractions, migrating to the cathode: a, b and c. Only fraction b is biologically active (Fig. 5).



Fig. 5. Scheme for the separation of albomycin by the method of electrophoresis on paper.

■—biologically active fraction;  
 ==—biologically inactive fraction.

Subsequent chromatographing of these fractions in a direction perpendicular to the electrophoretic separation in the system butanol-water-acetic acid (3:2:1) gave the following results: fractions a and c were homogeneous and did not separate; fraction b separated into 3 substances, of which only one exhibited biological activity (also see Fig. 3).

Separation of albomycin by the method of preparative electrophoresis-chromatography. A solution of 100 mg of albomycin in 0.5 ml of water was deposited on the upper portion of a cellulose column in 2 hr. Then the system was filled with 30%  $\text{CH}_3\text{COOH}$  and a current was passed through it for 3–3.5 days (220 v, potential gradient 4 v/cm). Since the material was colored, its separation into fractions could be observed directly. After separation had been achieved, the fractions were eluted from the column using buffer solution. The solutions of the different fractions were carefully evaporated to dryness, after which the residues were dissolved in a little water (1–2 drops) and then deposited on the chromatographic paper as a narrow band along the front. After passage of the solvent (butanol-water-acetic acid in the ratio 3:2:1), the chromatogram was dried and the separation was repeated once more in the same system. The fractions, obtained as bands on the chromatogram, were cut out and eluted with a little water (5–10 ml). The amount of albomycin in the different fractions varied from sample to sample and consequently has no practical significance.

Hydrolysis of albomycin. A solution of 250 mg of albomycin in 20% hydrochloric acid was heated under reflux on the water bath for 24 hr. The insoluble material was removed by filtration, while the filtrate was evaporated in vacuo to dryness until all of the hydrochloric acid had been removed. Anhydrous chloroform was used to extract the pyrimidine base from the residue. The chloroform extract was evaporated in vacuo. We obtained 10 mg (50%) of crystalline substance with m.p. 165–167°C. After recrystallization from water, m.p. 170–172°C. The reaction with p-diazobenzenesulfonic acid was positive. The substance exhibits a characteristic ultraviolet absorption spectrum (Fig. 4). Chromatographing of the substance in the 3 indicated systems gave the values shown in Table 1.

The hydrolysis of active fraction 2 (Table 2 and Fig. 3) was carried out in a similar manner. The uracil derivative was isolated in amounts sufficient only for chromatographing and spectrophotometry. The data obtained for it were the same as those described above.

#### SUMMARY

1. Two N-substituted pyrimidine bases, 1-methyluracil and 3-methyluracil, were synthesized.
2. Albomycin was separated into 5 fractions, and a preliminary characterization of these fractions was given.
3. A pyrimidine base was isolated from the acid hydrolyzates of albomycin and its active fraction which was identified as being 1-methyluracil.

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## STUDIES IN THE ALLO-AND ISOALLOXAZINE SERIES

### III. SYNTHESIS OF THIORIBOFLAVIN AND THIO ANALOGS OF ALLOXAZINE

V. M. Berezovskii and L. M. Mel'nikova

All-Union Institute of Vitamin Research

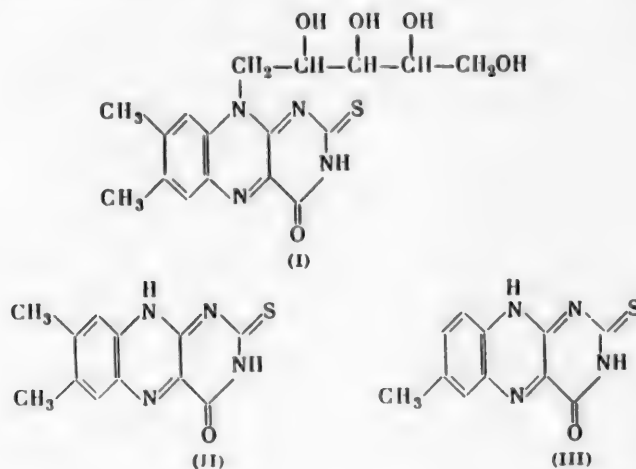
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 11,

pp. 3827-3831, November, 1961

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It seemed of interest to obtain some compounds of the allo and isoalloxazine series, in which the keto group in the 2 position is replaced by the thiono group, and study their biological activity. In synthesizing the thio analogs it was important to determine if they could be obtained by the condensation of aromatic o-aminoazo compounds with thiobarbituric acid. The condensation of o-aminoazo dyes with compounds containing an active ketomethylene group has been successfully applied to the preparation of compounds of the naphthopyrazine [1], imidazole [2] and isoalloxazine series [3]. Recently, compounds of the alloxazine series were obtained by this method for the first time [4].

The condensation of 2-thiobarbituric acid with 3,4-dimethylphenyl-6-phenylazo-N-D-ribitylamine, 3,4-dimethyl-6(3',4'-dimethylphenylazo)-aminobenzene and 4-methyl-6-(4'-tolylazo)aminobenzene in either boiling butyl acetate or butanol, in the presence of glacial acetic acid, gave us respectively 2-thioriboflavin (I), 2-thioluminchrome (II) and 6-methyl-2-thioalloxazine (III).



It was established that in contrast to riboflavin, luminchrome and 6-methylalloxazine, their 2-thio analogs do not exhibit fluorescence in ultraviolet light. A characteristic property of the obtained thioallo- and thioisoalloxazines is their ability to replace the sulfur by oxygen when treated with oxidizing agents like dilute hydrogen peroxide or atmospheric air in either acid aqueous or alcohol solution and change over to the corresponding strongly fluorescent allo- and isoalloxazines. Thus, the oxidation of 2-thioriboflavin (I) with dilute hydrogen peroxide easily gave riboflavin in crystalline form, which unequivocally proved the structure of 2-thioriboflavin as being a 6, 7-dimethylisoalloxazine with a ribityl chain in the 9 position, where either the thiono or the thiol group is found in the 2 position. Proof that the 2-thioallo- and 2-thioisoalloxazines have the thiono structure follows from their infrared absorption spectra, which are characterized by the absence of the bands of the SH group ( $2500-2600\text{ cm}^{-1}$ ) (Fig. 1).

Because of the great sensitivity of the oxidation reaction and the ability to determine riboflavin from its yellow-green fluorescence in ultraviolet light in an amount as little as 0.4  $\gamma$  in one milliliter, the thioriboflavin can be used

as a reagent for detecting traces of peroxides in organic compounds, for example, in dioxane, etc.

The oxidation of 2-thiolumichrome (II) and 6-methyl-2-thioalloxazine (III) also gave respectively lumichrome and 6-methylalloxazine which was proved by paper chromatography (Fig. 2).

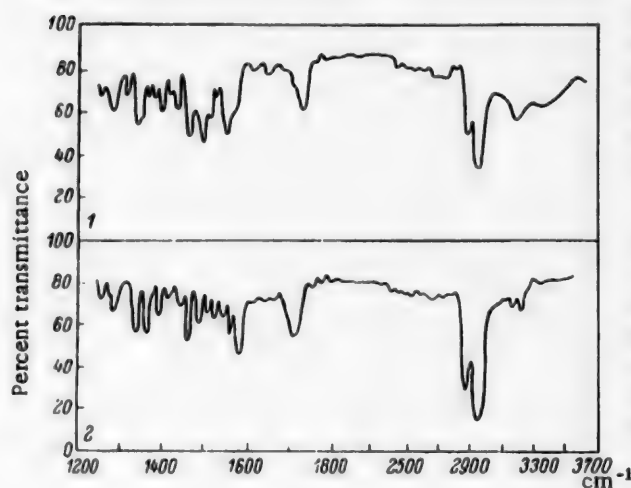


Fig. 1. Infrared absorption spectra. 1) 2-Thioriboflavin; 2) 2-thiolumichrome (IRS-11 spectrometer, NaCl and LiF prisms).

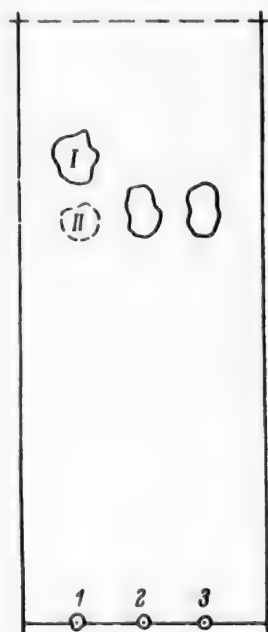


Fig. 2. Chromatogram of 2-thiolumichrome and its oxidation product. System: butanol-acetic acid-water (4:1:5); solvent-alcohol; 1) 2-thiolumichrome (I-non-fluorescent yellow spot; II-very faint bluish-white fluorescence); 2) 2-thiolumichrome, oxidized with  $H_2O_2$  to lumichrome (bluish-white fluorescence); 3) lumichrome (bluish-white fluorescence).

A strong deepening of the color occurs when the oxygen atom in the 2 position of the allo- or isoalloxazine ring is replaced by sulfur. In appearance, 2-thioriboflavin is a violet-red compound and 2-thiolumichrome and 6-methyl-2-thioalloxazine are yellow compounds, in contrast to the orange-yellow riboflavin and the pale yellow lumichrome.

The absorption spectra of the obtained thio compounds are quite different from the absorption spectra of the allo- and isoalloxazines, although they resemble each other quite closely in shape (Figs. 3 and 4). Replacing the oxygen by sulfur causes a greater bathochromic shift of the absorption bands. Thus, for 2-thioriboflavin when compared with riboflavin the 1st absorption maximum shifts by 7 m $\mu$  toward longer wavelengths and the intensity of absorption is reduced by 21%; the 2nd maximum is shifted by 51 m $\mu$  and the reduction in  $\epsilon$  is 22%; the 3rd maximum shifts by 28 m $\mu$  and the reduction in  $\epsilon$  is 32%; the 4th maximum shifts by 45 m $\mu$  and the increase in the intensity of absorption is 49%. The presence of the sulfur atom in the altered riboflavin molecule also explains the appearance of a new small maximum at 270 m $\mu$  (Fig. 3). The absorption spectra of the 2-thioalloxazines when compared with lumichrome embody approximately the same rules relative to the shifts in the maxima (Fig. 4).

When tested on young, vitamin-deficient, white rats weighing 38-45 g, 2-thioriboflavin in doses of 10  $\gamma$  per day exhibited the activity of vitamin  $B_2$ , stimulating the growth of the animals the same as the corresponding doses of riboflavin. It is possible that the vitamin activity of 2-thioriboflavin is explained by its oxidation in the organism to riboflavin.

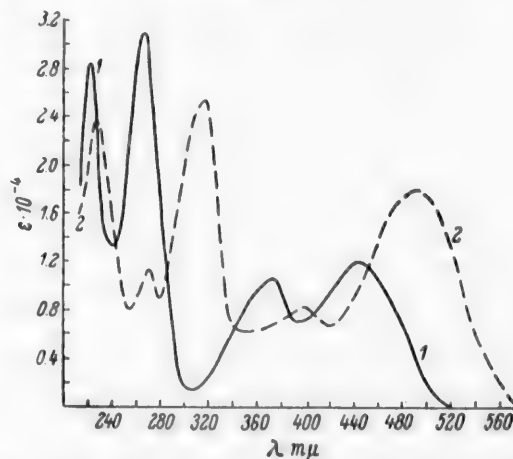


Fig. 3. Absorption spectra of riboflavin and thioriboflavin (in 0.006 n HCl). 1) Riboflavin; 2) thioriboflavin.

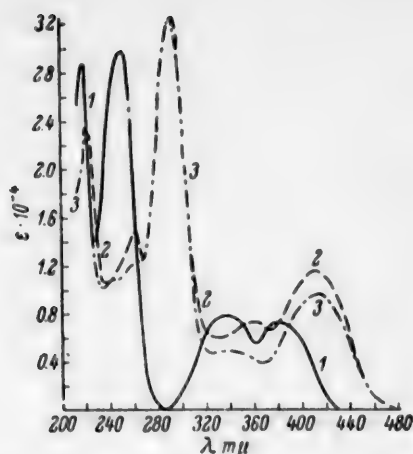


Fig. 4. Absorption spectra of alloxazine and its thio analogs (in alcohol). 1) Lumichrome; 2) 2-thiolumichrome; 3) 6-methyl-2-thioalloxazine.

Absorption spectrum (in 0.006 N HCl):  $\lambda_{\max}$  230 m $\mu$  ( $\epsilon$   $2.35 \cdot 10^4$ ), 317 m $\mu$  ( $\epsilon$   $2.54 \cdot 10^4$ ), 400 m $\mu$  ( $\epsilon$   $1.80 \cdot 10^4$ ) and 490 m $\mu$  ( $\epsilon$   $1.79 \cdot 10^4$ ).

Found %: C 51.88; H 5.21; N 13.72; S 8.19.  $C_{11}H_{10}O_5N_4S$ . Calculated %: C 52.03; H 5.14; N 14.28; S 8.17.

$R_f$  0.39 [in the system butanol-acetic acid-water (4:1:5)]; the thioriboflavin was deposited on the chromatogram in ethylene glycol solution].

From the reaction mother liquor we isolated 2.54 g of unreacted azo compound.

**Riboflavin and 2-thioriboflavin.** Two milliliters of 27% perhydrol solution was added slowly, at 25–30°C, to a solution of 1 g of 2-thioriboflavin in 4 ml of conc. hydrochloric acid. The precipitate was filtered and the filtrate was poured into 50 ml of boiling distilled water. After cooling and standing, we obtained 0.6 g (62.5%) of riboflavin as orange-yellow crystals with m.p. 282°C (decompn.), corresponding to a purity of 100% when analyzed by the fluorometric method [6]; from the literature [7]: m.p. 280°C (decompn.).

Absorption spectrum (in 0.006 N HCl):  $\lambda_{\max}$  223 m $\mu$  ( $\epsilon$   $2.85 \cdot 10^4$ ) 266 m $\mu$  ( $\epsilon$   $3.10 \cdot 10^4$ ) 372 m $\mu$  ( $\epsilon$   $1.06 \cdot 10^4$ ) and 445 m $\mu$  ( $\epsilon$   $1.20 \cdot 10^4$ ); these results are in agreement with the literature data [8].

$R_f$  0.31 [in the system butanol-acetic acid-water (4:1:5)]; from the literature [9]:  $R_f$  0.33.

**6,7-Dimethyl-2-thioalloxazine [2-thiolumichrome] (II) and 6-methyl-2-thioalloxazine (III).** The compounds were obtained by the respective condensation of 3, 4-dimethyl-6-(3',4'-dimethylphenylazo)-aminobenzene [10] and 4-methyl-6-(4'-tolylazo)aminobenzene [11] with 2-thiobarbituric acid under the above-described conditions. The technical products were washed first with hot ethylene glycol (120°C) and then with ethyl alcohol.

From 3 g of 3, 4-dimethyl-6-(3', 4'-dimethylphenylazo)aminobenzene and 2.72 g of 2-thiobarbituric acid we obtained 2.43 g (79.7 %) of 2-thiolumichrome (II) as yellow prisms with m.p. above 350°C.

Absorption spectrum (in alcohol):  $\lambda_{\max}$  224 m $\mu$  ( $\epsilon$   $2.30 \cdot 10^4$ ), 293 m $\mu$  ( $\epsilon$   $3.25 \cdot 10^4$ ), 360 m $\mu$  ( $\epsilon$   $0.72 \cdot 10^4$ ) and 411 m $\mu$  ( $\epsilon$   $1.17 \cdot 10^4$ ).

Found %: C 55.51, 55.48; H 4.46, 4.34; S 12.38.  $C_{12}H_{10}ON_4S$ . Calculated %: C 55.80; H 3.9; S 12.41.

$R_f$  0.80 (in the same system as for the thioriboflavin).

From 3 g of 4-methyl-6-(4'-tolylazo)aminobenzene and 3.07 g of 2-thiobarbituric acid we obtained 2.39 g (73.5%) of 6-methyl-2-thioalloxazine (III) as bright yellow prisms with m.p. above 300°C.

Absorption spectrum (in alcohol):  $\lambda_{\max}$  222 m $\mu$  ( $\epsilon$   $2.35 \cdot 10^4$ ), 292 m $\mu$  ( $\epsilon$   $3.27 \cdot 10^4$ ), 342 m $\mu$  ( $\epsilon$   $0.49 \cdot 10^4$ ) and 414 m $\mu$  ( $\epsilon$   $0.98 \cdot 10^4$ ).

Found %: C 53.71; H 3.79; S 12.38.  $C_{11}H_9ON_4S$ . Calculated %: C 54.09; H 3.28; S 13.11.

## EXPERIMENTAL

**6, 7-Dimethyl-9-(1'D-ribityl)-2-thioalloxazine [2-thioriboflavin] (I).** A mixture of 140 ml of butyl acetate, 16 g of 3, 4-dimethylphenyl-6-phenylazo-N-D-ribitylamine [5], 10 g of 2-thiobarbituric acid and 3.6 ml of glacial acetic acid was refluxed for 3 hr. The reaction mixture was filtered hot, and the precipitate was washed first with 50 ml of hot alcohol and then with 100 ml of boiling water. We obtained 11.83 g of precipitate, which was dissolved in 36 ml of conc. hydrochloric acid, filtered, and the solution was poured with stirring into 620 ml of boiling distilled water. We obtained 8.9 g (60.4%) of 2-thioriboflavin as violet-claret red needles with m.p. > 360°C (with a copper sheen, caused by the surface oxidation of the material to riboflavin). Recrystallization from ethylene glycol gave 2-thioriboflavin as slender violet-red needles. For analysis, the 2-thioriboflavin was washed by prolonged heating in boiling alcohol.

R<sub>f</sub> 0.78 (in the same system as for the thioriboflavin).

The authors wish to thank M. T. Ushakova for running the biological tests and L. V. Luk'yanova for taking the infrared spectra.

#### SUMMARY

1. The 2-thio analog of riboflavin, exhibiting the activity of vitamin B<sub>2</sub>, and the 2-thio analogs of the 6-methyl and 6,7-dimethylalloxazines were synthesized for the first time.
2. It was shown that 2-thioriboflavin and the thio analogs of the substituted alloxazines do not fluoresce in ultraviolet light.
3. Thioriboflavin can be used as a reagent for detecting peroxides in organic compounds.

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## STUDIES IN THE ALLO- AND ISOALLOXAZINE SERIES

### IV. NEW SYNTHESIS OF 2'-DESOXYRIBOFLAVIN AND SYNTHESIS OF ITS 2-THIO ANALOG

V. M. Berezovskii and T. V. Eremenko

All-Union Institute of Vitamin Research

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Original article submitted August 5, 1960

Among the various methods for the synthesis of isoalloxazine compounds, the method of the reductive condensation of aromatic o-aminoazo compounds with oxypyrimidines, containing an active methylene group [1-3], attracts attention because of the convenience and simplicity of execution. In the present paper this method has been extended to the synthesis of 2'-desoxyriboflavin, and analog of vitamin B<sub>2</sub>, produced from the hydrogenated derivative of 2-desoxy-D-ribose. \*

Considerable difficulties were encountered at the start when we attempted to synthesize 2'-desoxyriboflavin by the reductive condensation method, due to the fact that the necessary o-aminoazo compound could not be obtained by direct azo-coupling in the ring (in contrast to the easy azo-coupling of 3, 4-dimethylphenyl-D-ribitylamine with diazobenzene [2, 5]). Only after making a special study of the rearrangement of diazoimino compounds to secondary o-aminoazo compounds [6] did we return to a continuation of this work and its successful completion.

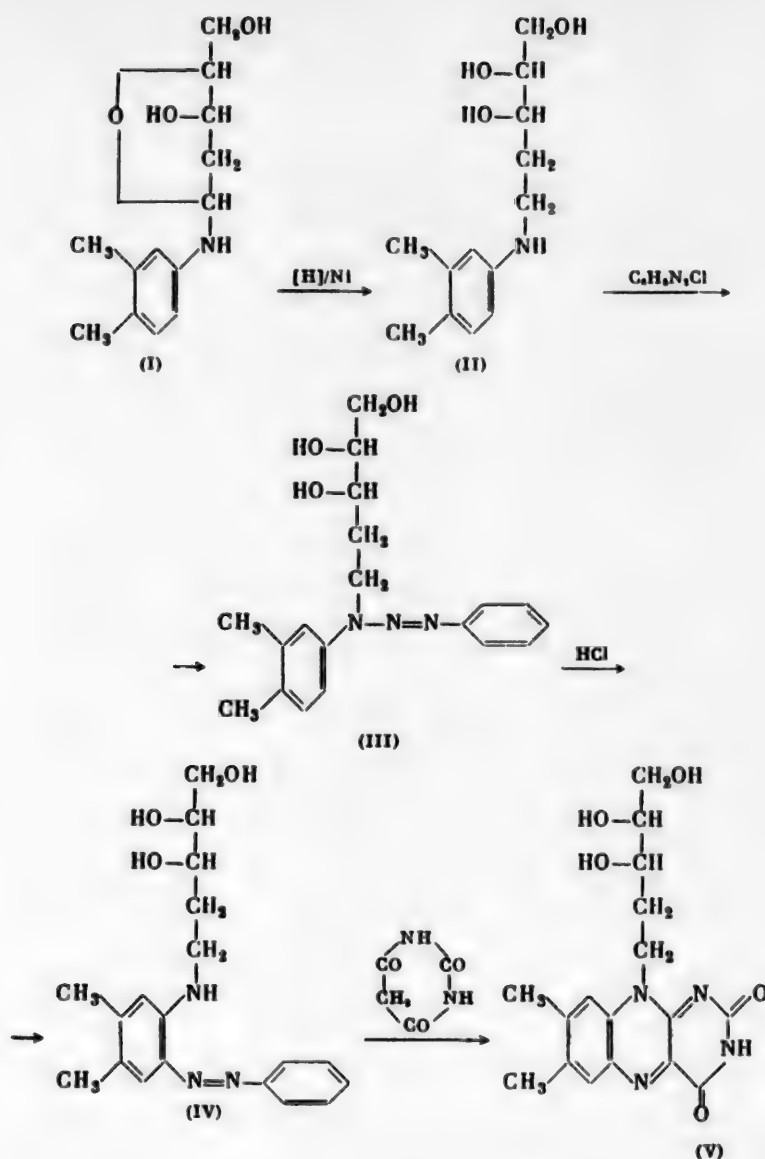
A new and convenient synthesis of 2'-desoxyriboflavin (V) was accomplished by reacting 3, 4-xylylidine-N-2'-desoxy-D-riboside (I), isolated from the reaction mixture containing 2-desoxy-D-ribose, with 3, 4-dimethylaminobenzene. It should be mentioned that if the N-glycosides of D-ribose and other pentoses, containing hydroxyls of erythro (cis)-configuration in positions 2 and 3, are characterized by the ability to form complex salts with sodium sulfate or other alkali metal salts [7, 8], which can be easily isolated from aqueous alcohol mixtures, then, as was established by us, the N-glycosides of 2-desoxy-D-ribose (with aniline or 3, 4-dimethylaminobenzene), in general not having a hydroxyl in the 2 position, do not form complex salts.

Compound (I), in the presence of skeletal nickel, was converted to 3, 4-dimethyl-N-2'-desoxy-D-ribitylamine (II), which was then coupled with diazobenzene in order to obtain 3, 4-dimethylphenyl-6-phenylazo-N-2'-desoxy-D-ribitylamine (IV). However, the reaction product proved to be the diazoimino compound (III), and not the azo compound (IV). As a result, the absence of a hydroxyl in the 2 position of the desoxyribityl substituent on the secondary amino group makes this substituent similar to a simple alkyl group, since, for example, N, 3, 4-trimethylaminobenzene forms hardly any azo dye when coupled with diazobenzene under similar conditions [9]. The o-aminoazo compound can be obtained in low yield from N, 3,4-trimethylaminobenzene if the azo-coupling with p-aminobenzoic acid is run in 85% formic acid [9].

To obtain the o-aminoazo compound (IV) we resorted to the rearrangement of the triazene (III) in alcohol medium, in the presence of hydrochloric acid; (IV) was obtained in 57.5% yield.

The condensation of o-aminoazo compound (IV) with barbituric acid in butyl acetate medium, in the presence of acetic acid as the catalyst, gave 2'-desoxyriboflavin (V).

\* 2'-Desoxyriboflavin was first synthesized in 1935 from 2-desoxy-D-ribose and 1-amino-2-carbethoxyamino-4, 5-dimethylbenzene through 4, 5-dimethyl-2-carbethoxyaminophenyl-N-2'-desoxy-D-ribitylamine by hydrolysis of the latter and subsequent condensation with alloxan [4].



The formation of this isoalloxazine (V) serves as simultaneous proof that the rearrangement of the diazoimino compound (III) yields an azo dye that in structure corresponds specifically to compound (IV), and not to the isomeric 3, 4-dimethylphenyl-2-phenylazo-N-2'-desoxy-D-ribitylamine, since it is known that secondary o-aminoazo compounds, with a methyl group in the ortho-position to the azo group, do not condense with barbituric acid [10].

2-Thio-2'-desoxyriboflavin was obtained from o-aminoazo compound (IV) and thiobarbituric acid by the procedure given in [11]. It is easily oxidized by hydrogen peroxide to 2'-desoxyriboflavin (V) which was shown by paper chromatography. Its absorption spectrum is similar to the absorption spectrum of 2-thioriboflavin [11].

#### EXPERIMENTAL

**3, 4-Xylidine-N-2'-desoxy-D-ribose (I).** A solution of 7.5 g of 1:2,5:6-diacetone-3-methylsulfonylglucose [12] in 150 ml of 50% methyl alcohol was heated in the presence of 1.5 ml of conc. sulfuric acid for 2 hr under reflux. After cooling, the reaction mass was neutralized with 2 N NaOH solution to pH 7.5-8.0, the sodium sulfate was filtered, and the filtrate was evaporated in vacuo to a small volume. Then about 30 ml of 1N NaOH solution was added in 4-5 hr, with stirring, at 50-60°, to the residue to a pH of 9 (using phenolphthalein [13]). The obtained solution was evaporated in vacuo to dryness; the residue was triturated with methyl alcohol and the sodium sulfate was filtered. The filtrate (15 ml) was treated with 7.5 ml of water and 4.1 g of 3, 4-dimethylaminobenzene. The

solution was kept for about an hour at a temperature of 0 to +3°C. The obtained precipitate was filtered and washed with cold methyl alcohol. Yield 1.45 g (29.6%); colorless plates with m.p. 153–154.5°C (decompn.) (from alcohol).  $[\alpha]_D^{25} + 143.7^\circ \text{C} \rightarrow + 95.8^\circ \text{C}$  (c 2, pyridine).

Found %: C 65.98, 65.83; H 7.97, 8.18; N 5.65.  $\text{C}_{15}\text{H}_{19}\text{O}_3\text{N}$ . Calculated %: C 65.80; H 8.07; N 5.90.

**3, 4-Dimethylphenyl-N-2'-desoxy-D-ribitylamine (II).** A solution of 3.25 g of riboside (I) in 60 ml of 80% alcohol was hydrogenated in the presence of 1.5 g of skeletal nickel in an autoclave at 40–50 atm and 38–45°C for 3 hr. After removal of the catalyst and evaporation of the filtrate to a small volume the obtained precipitate was filtered, washed with alcohol, and dried. Yield 2.96 g (90.5%); colorless needles with m.p. 109–110°C.  $[\alpha]_D^{25} + 25.5^\circ \text{C}$  (c 0.68, 2N HCl).

Found %: C 65.31; H 9.05; N 5.71, 5.95.  $\text{C}_{15}\text{H}_{21}\text{O}_3\text{N}$ . Calculated %: C 65.32; H 8.86; N 5.86.

**3-(3', 4'-Dimethylphenyl)-3-(2"-desoxy-1"-D-ribityl)-1-phenyltriazene (III).** A solution of 2.3 g of ribitylamine (II) in 20 ml of water and 2 ml of hydrochloric acid was mixed with a solution of phenyldiazonium chloride (from 1.31 g of aniline, 3 ml of hydrochloric acid and 1.02 g of sodium nitrite). Then 20 ml of 28% sodium acetate solution was added to the obtained solution with stirring, and after 15–20 min the obtained precipitate was filtered and washed well. We obtained 3.3 g (87%) of triazene (III) as lemon-yellow needles with m.p. 134.5–135°C (decompn.) (from alcohol).

Absorption spectrum (in alcohol):  $\epsilon$   $\begin{matrix} 236 \text{ m}\mu \\ \text{max} \end{matrix}$  16300;  $\epsilon$   $\begin{matrix} 268 \text{ m}\mu \\ \text{min} \end{matrix}$  2700;  $\epsilon$   $\begin{matrix} 352 \text{ m}\mu \\ \text{max} \end{matrix}$  16400.

Found %: C 66.86; 66.69; H 7.40, 7.24; N 12.54, 12.44.  $\text{C}_{19}\text{H}_{25}\text{O}_3\text{N}_3$ . Calculated %: C 66.45; H 7.34; N 12.23.

**3, 4-Dimethylphenyl-6-phenylazo-N-2'-desoxy-D-ribitylamine (IV).** A mixture of 2.45 g of triazene (III) and 0.5 g of 3, 4-dimethylphenyl-N-2'-desoxy-D-ribitylamine (II) in 32 ml of alcohol and 0.16 ml of conc. hydrochloric acid was heated for 3 hr at 35°C, then for 3 hr at 50–60°C and for 1 hr at 70°C, after which the reaction mass was evaporated in vacuo to half-volume, followed by the addition of 5 g of ice and then of 20 ml of hydrochloric acid with vigorous stirring. The precipitate of the hydrochloride was filtered, washed with hydrochloric acid, and then triturated with 25 ml of 25% ammonia solution. The obtained precipitate was filtered and washed with ammonia; weight 1.4 g (57.5%); orange-red needles collected as clusters. M.p. 129–130°C (from alcohol).

Absorption spectrum (in alcohol):  $\epsilon$   $\begin{matrix} 247 \text{ m}\mu \\ \text{max} \end{matrix}$  15100;  $\epsilon$   $\begin{matrix} 290 \text{ m}\mu \\ \text{min} \end{matrix}$  5900;  $\epsilon$   $\begin{matrix} 324 \text{ m}\mu \\ \text{max} \end{matrix}$  17200;  $\epsilon$   $\begin{matrix} 373 \text{ m}\mu \\ \text{min} \end{matrix}$  1600;

$\epsilon$   $\begin{matrix} 471 \text{ m}\mu \\ \text{max} \end{matrix}$  10800. Based on the maxima, the spectrum corresponds to the absorption spectrum of 3, 4-dimethylphenyl-6-phenylazo-N-D-ribitylamine.

Found %: C 66.39, 66.61; H 7.49, 7.47; N 12.01, 12.14.  $\text{C}_{19}\text{H}_{25}\text{O}_3\text{N}_3$ . Calculated %: C 66.45; H 7.34; N 12.23.

**6, 7-Dimethyl-9-(2'-desoxy-1'-D-ribityl)isoalloxazine (V).** A mixture of 2.6 g of azo compound (IV) and 1.54 g of barbituric acid in 35 ml of butyl acetate was heated in the presence of 3.4 ml of acetic acid for 5 hr under reflux. The obtained precipitate was filtered, washed with alcohol, then with boiling water (10 ml), and finally with cold water. The substance was purified as described in [2]. We obtained 1.8 g (65.4%) of 2'-desoxyriboflavin (V) as light-orange needles with m.p. 281–283°C (decompn.).

Absorption spectrum (in water):  $\epsilon$   $\begin{matrix} 223 \text{ m}\mu \\ \text{max} \end{matrix}$  28500;  $\epsilon$   $\begin{matrix} 240 \text{ m}\mu \\ \text{min} \end{matrix}$  14000;  $\epsilon$   $\begin{matrix} 266 \text{ m}\mu \\ \text{max} \end{matrix}$  28000;  $\epsilon$   $\begin{matrix} 304 \text{ m}\mu \\ \text{min} \end{matrix}$  2700;  $\epsilon$   $\begin{matrix} 372 \text{ m}\mu \\ \text{max} \end{matrix}$  9900;  $\epsilon$   $\begin{matrix} 398 \text{ m}\mu \\ \text{min} \end{matrix}$  6500;  $\epsilon$   $\begin{matrix} 445 \text{ m}\mu \\ \text{max} \end{matrix}$  10200.

2' Desoxyriboflavin is characterized by the same absorption maxima as riboflavin. In water solution it exhibits a visible yellow-green fluorescence, which is enhanced in ultraviolet light.

Found %: C 56.72, 56.57; H 5.76, 5.62; N 15.25, 15.21.  $\text{C}_{17}\text{H}_{20}\text{O}_5\text{N}_4$ . Calculated %: C 56.66; H 5.59; N 15.55.

The  $R_f$  values found for 2'-desoxyriboflavin are 0.74 (pyridine–isobutyl alcohol–acetic acid–water; 33:33:1:33) and 0.40 (butanol–acetic acid–water; 4:1:5), while for riboflavin the corresponding values are 0.71 and 0.31.

**2-Thio-2'-desoxyriboflavin.** A mixture of 1.68 g of azo compound (IV) and 1.45 g of thiobarbituric acid in 30 ml of butyl acetate was heated in the presence of 0.21 ml of acetic acid for 5 hr at a bath temperature of about 130°C. The obtained precipitate was filtered, washed with alcohol, then with boiling water, and finally with cold water. The substance was purified as described in [11]. Yield 1.28 g (69.6%); violet-red crystals with m.p. above 300°C.

Found %: N 14.75, 14.89; S 8.53, 8.80.  $C_{17}H_{20}O_4N_4S$ . Calculated %: N 14.88; S 8.52.

The product obtained from the oxidation of 2-thio-2'-desoxyriboflavin with dilute hydrogen peroxide in acid solution was chromatographed on paper to give a spot that exhibited yellow-green fluorescence in ultraviolet light and had  $R_f = 0.40$  (butanol-acetic acid-water; 4:1:5), corresponding to 2'-desoxyriboflavin.

#### SUMMARY

1. A new synthesis of 6, 7-dimethyl-9-(2'-desoxy-1'-ribityl)-isoalloxazine was accomplished by the condensation of 2-desoxyribose with 3, 4-dimethylaminobenzene, followed by reduction, coupling with diazobenzene to the diazoimino compound, rearrangement to the o-aminoazo compound, and condensation with barbituric acid.

2. It was shown that in its behavior in the coupling reaction (difficult azo-coupling in the ring), 3,4-dimethylaminobenzene, with an N-2'-desoxyribityl substituent, differs from compounds containing an N-ribityl radical, and behaves like a secondary amine with a simple alkyl substituent.

3. 2-Thio-2'-desoxyriboflavin and four other previously unknown compounds were synthesized.

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# SYNTHESES BASED ON SCLAREOL

## VI. SOME NEW PHYSIOLOGICALLY ACTIVE AMINO DERIVATIVES OF SCLAREOL

D. P. Popa and G. V. Lazur'evskii

Institute of Chemistry of the Moldavian Branch of the Academy of Sciences of the USSR

Translated from Zhurnal Obshchei Khimii, Vol. 31, No. 11, pp. 3835-3838, November, 1961

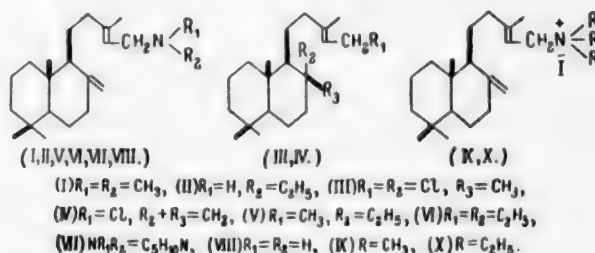
Original article submitted September 12, 1960

In the literature a relatively small number of papers is devoted to the synthesis of nitrogen-containing derivatives of terpenes. Nitrogen-containing bases of the terpene series, being peculiar alkaloidlike compounds, must be considered as being a class of compounds with a highly promising future from the practical standpoint. Among them there already exist compounds possessing valuable physiological properties [1-4], plasticizers and insecticides [5], antioxidants and dye intermediates [6], and other valuable substances.

The present paper is devoted to the least studied field in this respect—the synthesis and study of the diterpene nitrogen-containing bases of the sclareol series.

In previous papers [7] we described the synthesis of the N-dimethyl- and N-ethyl-15-amino- $\Delta^8(20), 13(14)$ -sclarodienes (I) and (II), as intermediates for the synthesis of quaternary ammonium salts. As the pharmacological testing revealed, the hydrochlorides of these amines exhibit a weak toxicity and a high spasmolytic activity, while the quaternary ammonium salts are good bactericides. This information caused us to prepare a series of amino derivatives of sclareol for the purpose of establishing the relationship existing between their structure and the activity.

In addition to the described amines (I) and (II), we synthesized the following new bases and their salts: N-methylethyl- (V) and N-diethyl-15-amino- $\Delta^8(20), 13(14)$ -sclarodiene (VI) and 15-amino- $\Delta^8(20), 13(14)$ -sclarodiene (VIII). The methylation of base (I) gave trimethylsclarodienylammonium iodide (IX), while the ethylation of base (VI) gave triethylsclarodienylammonium iodide (X), differing from (IX) by a greater solubility in water. Bases (I–VIII) were prepared from 8, 15-dichloro- $\Delta^8(20), 13(14)$ -sclarene (III) and 15-chloro- $\Delta^8(20), 13(14)$ -sclarodiene (IV), described by us previously [8].



In all cases the condensation of the chloride with the amines goes with the formation of a heptacyclic double bond at carbon atom 8; the yields of the end products are high. Only primary amine (VIII) is obtained in poorer yield, does not give a crystalline hydrochloride, and can be purified only through the oxalate. All of the bases are liquids, decomposing when distilled in a vacuum as low as 0.1 mm, but when distilled in a higher vacuum (of the order of 0.04–0.01 mm) they distill well up to temperatures of 140°C.

Preliminary studies on the spasmolytic properties of the hydrochlorides revealed that these compounds exhibit a higher activity than papaverine.



A study of the antibacterial activity of trimethylsclarodienylammonium iodide (IX), made by S. I. Zelenukh, revealed that this compound in a dilution of 1:1,000,000 inhibits the growth of such microorganisms as *Staphylococcus aureus*, *Micrococcus catarrhalis*, *Actinomyces griseus*, etc.

#### EXPERIMENTAL

**N-Methylethyl-15-amino- $\Delta^8(20),13(14)$ -sclarodiene (V).** A solution of 1.2 g of base (II) in 8 ml of acetone was treated with 2 ml of freshly distilled methyl iodide. The mixture was heated under reflux for 1 hr on the water bath, and then was allowed to stand for 20 hr at room temperature. After this the acetone and excess methyl iodide were removed by distillation. The residue was treated with 5 ml of dry acetone, and then with 10 ml of dry ether. The obtained fine precipitate, darkening when allowed to stand, was filtered and then shaken with 10 ml of 10% NaOH solution. The base was extracted twice with ether. The ether solution was washed with water and then dried over sodium sulfate. A stream of dry hydrogen chloride was passed through the dry ether solution. Here a finely crystalline powder deposited. Yield 0.8 g. After recrystallization from acetone, m.p. 174–176°C (decompn.).

Found %: C 75.21, 74.98; H 11.31, 11.53; N 3.92, 3.86; Cl 9.35, 9.29.  $C_{23}H_{41}N \cdot HCl$ . Calculated %: C 75.09; H 11.42; N 3.81; Cl 9.68.

**N-Diethyl-15-amino- $\Delta^8(20),13(14)$ -sclarodiene (VI).** A mixture of 2 g of dichloride (III) and 6 ml of diethylamine in 20 ml of alcohol was heated under reflux for 2 hr on the water bath, and then allowed to stand overnight at room temperature. After this the alcohol and excess diethylamine were removed by distillation. The residue was stirred twice with 10 ml of ether and the ether layer was separated by decantation. Then the residue was treated with 10 ml of 10% NaOH solution, followed by extraction of the oil layer with 5 ml of ether. The combined ether solutions were washed 3 times with water, and then 5 times with 5 ml portions of 10% hydrochloric acid. The ether solution was washed with water, dried over sodium sulfate, and then a stream of dry hydrogen chloride was passed through the dry ether solution. The obtained finely crystalline precipitate was filtered and then recrystallized from acetone. We obtained 1.8 g of the hydrochloride with m.p. 185–186°C.

Found %: C 75.70, 75.73; H 11.77, 11.76; N 3.75, 3.95; Cl 9.06, 9.22.  $C_{24}H_{43}N \cdot HCl$ . Calculated %: C 75.50; H 11.53; N 3.67; Cl 9.30.

The hydrochloride (0.8 g) was shaken with 5 ml of 10% NaOH solution and the base was extracted with ether. The ether solution was dried, and the ether was removed by distillation. The residue was vacuum-distilled. We obtained 0.5 g of colorless liquid. B.p. 134–136°C at 0.04 mm,  $n_D^{18}$  1.5085.

Found %: C 83.33, 83.03; H 12.40, 12.46; N 4.01, 4.19.  $C_{24}H_{43}N$ . Calculated %: C 83.49; H 12.47; N 4.06.

**Preparation of base (VI) from monochloride (IV).** A mixture of 4 g of the oil obtained from the mother liquors after removal of dichloride (III), containing the monochloro derivative (IV), 15 ml of alcohol and 5 ml of diethylamine was heated in a steel bomb for 3 hr at 78–80°C, and then was allowed to stand overnight at room temperature. Further treatment was the same as described above. We obtained 1.6 g of the hydrochloride of base (VI) with m.p. 185–186°C. The mixed melting point with the above described hydrochloride was not depressed.

**Piperidyl- $\Delta^8(20),13(14)$ -sclarodiene (VII).** A mixture of 1 g of dichloride (III) and 5 ml of piperidine was heated under reflux for 1.5 hr. The mixture was allowed to stand for 40 hr at room temperature. Then 15 ml of ether was added, the piperidine hydrochloride was filtered, the precipitate was washed with an additional 5 ml of ether, and the combined ether solutions were washed several times with water. The washed ether solution was then treated with 5% hydrochloric acid until acid to Congo red. Here the liquid separated into three layers: upper—ether, lower—aqueous acid, containing the piperidine salt, and middle—a yellow oil that represented the crude hydrochloride of base (VII), difficultly soluble in water. The lower layer was separated, and the remainder was washed again with acid, followed by the addition of 15 ml of 5% NaOH solution, as a result of which the lower layer went into the ether layer. The ether solution was washed with water, dried over sodium sulfate, and then a stream of dry hydrogen chloride was passed through it. This resulted in the deposition of a viscous oil that could not be made to crystallize. The ether was vacuum-distilled, while the residue was washed with a little dry ether and allowed to stand in the cold. After several hours the mass began to crystallize. This mass was stirred with 10 ml of absolute ether to give a white, sticky precipitate, which was filtered and then dried in a desiccator over  $P_2O_5$ , where it changed to a fine powder. Recrystallization from dioxane gave 0.8 g of finely crystalline compound, m.p. 178–180°C (decompn.).

Found %: C 76.06, 75.97; H 11.39, 11.36; N 3.26, 3.29; Cl 9.21, 9.35.  $C_{25}H_{45}N \cdot HCl$ . Calculated %: C 76.25; H 11.19; N 3.56; Cl 9.02.



Base (VII) was obtained from the hydrochloride using the procedure described above.

15-Amino- $\Delta^8(20),13(14)$ -sclarodiene (VIII). A mixture of 1 g of dichloride (III) and 8 ml of ethanol, saturated with ammonia, was heated in a steel bomb for 3 hr at 75-78°C, and then allowed to stand for 15 hr at room temperature. After opening the bomb, the alcohol and excess ammonia were vacuum-distilled. The base was separated from ammonium chloride by extracting 3 times with ether. The ether solution was washed with water and then dried over sodium sulfate. The passage of hydrogen chloride into the dry ether solution gave a brown oil that could not be made to crystallize. This oil was soluble in ether when made alkaline with 10% NaOH solution. The separated ether layer was treated with a saturated ether solution of oxalic acid until acid to litmus. Here a finely crystalline precipitate was obtained which proved to be insoluble in water. Recrystallization from alcohol gave 0.25 g of substance with m.p. 143-145°C.

When the oxalate was shaken with a mixture of 10% NaOH solution and ether the suspension slowly disappeared, and the free base (VIII) went into the ether layer. The free base was a yellow liquid with a characteristic odor, giving qualitative tests for an alkaloid with Dragendorff reagent and with silicotungstic acid. B.p. 128-130°C at 0.04 mm.

Found %: N 4.61, 4.55.  $C_{20}H_{25}N$ . Calculated %: N 4.84.

Trimethyl- $\Delta^8(20),13(14)$ -sclarodienylammonium iodide (IX). A mixture of 1 g of base (I), 10 ml of acetone and 5 ml of methyl iodide was heated under reflux for 0.5 hr on the water bath, and then the mixture was allowed to stand at room temperature for 20 hr. The excess methyl iodide and the acetone were removed by distillation, while the solid residue was recrystallized from acetone. We obtained 1.2 g of the substance as needle crystals. M.p. 194-195°C (decompn.).

Found %: C 60.36, 60.34; H 9.37; N 2.92, 3.22; J 27.13, 27.43.  $[C_{20}H_{25}N]^+J^-$ . Calculated %: C 60.13; H 9.15; N 3.05; J 27.67.

Triethyl- $\Delta^8(20),13(14)$ -sclarodienylammonium iodide (X). A mixture of 1 g of base (VI), 10 ml of acetone and 5 ml of ethyl iodide was heated on the water bath, in the same manner as described for compound (IX). The residue from the removal of the solvent was reprecipitated twice from acetone solution with ether, and then it was recrystallized from acetone. We obtained 1.3 g of crystalline substance. M.p. 139-140.5°C (decompn.).

Found %: C 62.40, 62.37; H 9.91, 9.92; N 2.90, 2.95; J 25.87, 25.69.  $[C_{20}H_{25}N]^+J^-$ . Calculated %: C 62.29; H 9.58; N 2.79; J 25.35.

#### SUMMARY

Some new diterpene nitrogen-containing bases of the sclareol series were obtained by the reaction of certain amines with 8, 15-dichloro- $\Delta^{13(14)}$ -sclarene and 15-chloro- $\Delta^8(20),13(14)$ -sclarodiene. The hydrochlorides of these bases display spasmolytic activity, while the quaternary ammonium salts manifest good antibacterial activity.

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PECULIAR MANIFESTATION OF THE ORTHO-EFFECT  
IN THE THIOINDOGENIDE SERIES

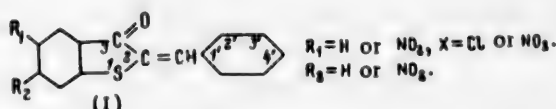
V. A. Izmail'skii and M. A. Mostoslavskii

Laboratory of Dyes and Color Problems of the V. I. Lenin Moscow  
Pedagogical Institute and the Rubezhan Branch of the Scientific  
Research Institute of Organic Intermediates and Dyes

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p. 3839, November, 1961

Original article submitted July 17, 1961

In the process of studying the phototropy of thioindogenides, explained by photochemical cis-trans-isomerization [1], the need arose to investigate the influence of ortho-substituents, found in the vicinity of the central double bond. It proved that the irradiation of solutions of 2'-chloro- or 2'-nitrothioindogenides of general formula (I), prepared in the dark, resulted not only in photochemical cis-trans-isomerization, but also in a fundamental and irreversible photochemical change in the compounds. The corresponding p-substituted derivatives are much more stable to the action of light.



It was also established that 2-(2',4'-dichlorobenzylidene)-3-keto-2,3-dihydrothianaphthene is decomposed when its solution is irradiated at the same rate as 2-(2'chlorobenzylidene)-3-keto-2,3-dihydrothianaphthene; 2-(2',6'-dichlorobenzylidene)-3-keto-2,3-dihydrothianaphthene is decomposed at a rate nearly 10 times as fast.

In contrast to the 2'-chloro and 2'-nitro derivatives, the 2'-methoxy- and 2'-hydroxythioindogenides do not undergo a rapid photochemical decomposition. Further studies will show whether this is due to the smaller volume of the hydroxy and methoxy groups (when compared with the chlorine or nitro group) and steric influences, or to the difference in the chemical character of the substituents.

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CONCERNING THE PAPER BY JOLIVET "STUDY OF THE ANHYDRIDE  
OF 3, 6-ENDOÖXY- $\Delta^4$ -TETRAHYDROPHTHALIC ACID"

Yu. K. Yur'ev and N. S. Zefirov

Moscow State University

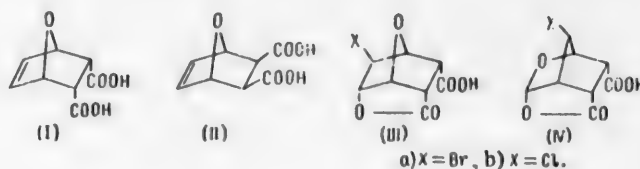
Translated from *Zhurnal Obshchei Khimii*, Vol. 31, No. 11,

pp. 3840-3841, November, 1961

Original article submitted July 3, 1961

The paper by Jolivet [1], representing a generalization of the early investigations of this author [2,3] and devoted to a study of some of the problems connected with the halogenation and reduction of the derivatives obtained from the adduct of furan with maleic anhydride, attracted our attention in connection with the preparation of a paper on the Wagner-Meerwein rearrangement in the 3, 6-endoöxycyclohexane series during halogenation. Quite a few papers have been devoted to the halogenation of compounds in this series, which have made it possible to explain some of the stereochemical problems relating to the course of the diene synthesis in the furan series. However, in the indicated paper by Jolivet the problems relating to the stereochemistry of the starting compounds are not taken into consideration, and this had led to errors in determining the structure of the compounds obtained by him.

From the literature it is known that the reaction of furan with maleic acid leads to a mixture of the endo- and exo-adducts (I and II, respectively), in which connection the endo-bromolactone (IIIa) can be isolated when this mixture is brominated, being the derivative of the endo-form of the adduct [4,5]. Woodward and Baer [6] have shown that the adduct of furan with maleic anhydride is the exo-form; it is obvious that the hydrolysis of this adduct will yield the exo-acid (II), the bromination of which takes place with rearrangement and leads to bromolactone (IVa).



By-passing the stereochemical side of the problem, Jolivet assumes that Diels and Alder [4] obtained bromolactone (IIIa) by the bromination of the acid, obtained in turn by the hydrolysis of the adduct of furan with maleic anhydride, whereas actually this acid, in view of what has said above, is the exo-form. As a result of this incorrect interpretation of the literature data, Jolivet assigns an erroneous structure to the product of the chlorination of (II) in aqueous medium. Chlorolactone (IVb) should be obtained in this reaction, whereas Jolivet assigns its the structure of (IIIb). We ran the chlorination of (II) under the conditions indicated by Jolivet and found that chlorolactone (IVb) (m.p. 210-220°C with decomposition, depending on the rate of heating) is actually obtained in this reaction, since it, the same as (IVa), but in contrast to (IIIa), gives a positive test when heated with either Fehling or Tollen's reagent.

In a similar manner, the bromination of (II) using the N-bromoimide of 3, 6-endoöxyhexahydrophthalic acid should give bromolactone (IVa), and not bromolactone (IIIa), as was found by Jolivet. We also repeated this experiment and found that the reaction product is actually (IVa), the constants (m.p. 153°C with decompn.) and properties of which coincided with those reported in the literature.

Also erroneous is the treatment of the formation of bromolactone (IIIa) through the corresponding bromohydrin, stable at room temperature and giving bromolactone (IIIa) when heated to 100°C in vacuo. Berson [7] was able to show spectroscopically that lactones, containing water of crystallization, are analogous compounds. As a result, the process of cleaving water from such compounds is a process of cleaving water of crystallization and not a process of lactonization of the bromohydrin.

It is possible that the presence of water of crystallization led the author of the discussed paper to err when he studied the oxidation of the furan-maleic anhydride adduct with peroxyformic acid. As was shown by us [8, 9], this reaction leads to the corresponding  $\alpha$ -oxide, whereas Jolivet erroneously assigns the structure of the diol to the oxidation product. Therefore it is not surprising that the "diol" obtained by Jolivet can be neither acetylated nor benzoylated, and does not give a derivative with either phenyl or naphthyl isocyanate.

We also consider as doubtful the obtaining of 1, 2-bis(hydroxymethyl)-3,6-endoxy-4,5-cyclohexanedione when 1, 2-bis(hydroxymethyl)-3,6-endoxy-4-cyclohexene is oxidized with peroxyformic acid. The author does not support such an unusual reaction course by citing literature analogies, and characterization of the obtained product is based entirely on the elemental analysis data. Based on the analysis data, the obtained  $\alpha$ -diketone is not the hydrated form and at the same time it is a colorless compound, although, as it is known, analogous  $\alpha$ -diketones are colored compounds; in addition, no proof is offered for the presence of carbonyl groups in the substance.

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## Soviet Journals Available in Cover-to-Cover Translation

[illegible]

continued

Izv. AN SSSR, Of(td), T(ekhn), N(auk): Met(ali), i top.	(see Met. i top.) Izvestiya Akademii Nauk SSSR: Seriya fizicheskaya	Bulletin of the Academy of Sciences of the USSR: Physical Series	1	1954
Izv. AN SSSR Ser. fiz(ich).	Izvestiya Akademii Nauk SSSR: Seriya geofizicheskaya	Bulletin (Izvestiya) of the Academy of Sciences USSR: Geophysics Series	1	1954
Izv. AN SSSR Ser. geofiz.	Izvestiya Akademii Nauk SSSR: Seriya geofizicheskaya	Izvestiya of the Academy of Sciences of the USSR: Geologic Series	1	1958
Izv. AN SSSR Ser. geol.	Izvestiya Akademii Nauk SSSR: Seriya geologicheskaya	Soviet Rubber Technology	18	1959
Kauch. i rez.	Kauchuk i rezina	Kinetics and Catalysis	1	1960
	Kinetika i kataliz	Coke and Chemistry USSR	3	1960
	Koks i khimiya			
Kolloidn. zh(urn).	Kolloidnyi zhurnal	Colloid Journal	1	1958
	Kristallografiya	Soviet Physics - Crystallography	1	1958
Metallov. i term. obrabot. meta.	Metallovedeniye i termicheskaya obrabotka metallov	Soviet Physics - Crystallography Metals	14	1952
			2	1957
Met. i top. Mikrobiol. OS	Metallurgiya i topliva Mikrobiologiya Optika i spektroskopiya Pochvovedeniye Priboirostroenie	Russian Metallurgy and Fuels Microbiology Optics and Spectroscopy Soviet Soil Science Instrument Construction	6	1958
			26	1957
			6	1959
			1	1956
Priboiry i tekhn. eksperimenta)	Priboiry i tekhnika eksperimenta	Instruments and Experimental Techniques	1	1959
Prikl. matem. i mekh.	Prikladnaya matematika i mekhanika	Applied Mathematics and Mechanics	1	1957
PTÉ	(see Priboiry i tekhn. éks.) Problemy Severa		1	1958
Radiolekh.	Radiolekhika	Problems of the North	12	1957
Radiolekh. i elektronika	Stanki i instrument	Radio Engineering and Electronics Machines and Tooling	2	1957
	Stal'	Stal' (in English)	1	1959
Stek. i keram.	Steklo i keramika	Glass and Ceramics	1	1959
Svaroch. proizvo.	Svarochnoye proizvodstvo	Welding Production	13	1956
Teor. veroyat. i prim.	Teoriya veroyatnostey i ee primeneniye	Theory of Probability and Its Applications	4	1959
Tsvetn. Metall	Tsvetnyye metall	Nonferrous Metals	1	1956
UFN	Uspekhi fizicheskikh Nauk	Soviet Physics - Uspekhi (partial translation)	1	1960
UKh	Uspekhi khimii	Russian Chemical Reviews	66	1958
UMN	Uspekhi matematicheskikh nauk	Russian Mathematical Surveys	1	1960
Usp. fiz. nauk	(see UFN)		15	
Usp. khim(ii)	(see UMN)			
Usp. matem. nauk	Usp. khim(ii)			
Usp. sovr. biol.	Usp. matem. nauk			
Vest. mashinostroeniya	Vestnik mashinostroeniya			
Vop. gem. i per. krovi	Voprosy gematologii i perekrivaniya krovi			
Vop. onk.	Voprosy onkologii			
Vop. virusol.	Voprosy virusologii			
Zavodsk. lab(oratoriya)	Zavodskaya laboratoriya			
ZhAKh Zh. anal(it), khimii	Zhurnal analiticheskoi khimii			
ZhETF	Zhurnal éksperimental'noi i teoreticheskoi fiziki			
ZhFKh Zh. fiz. khimii	Zhurnal fizicheskoi khimii			
ZhMEL Zhurn. mikrobiol. épidemiol. i immunobiol.	Zhurnal mikrobiologii, épidemiologii i immunobiologii			
ZhNKh	Zhurnal neorganicheskoi khimii			
Zh(urn), neorgan(ich). khim(ii)				
ZhOKh	Zhurnal obshchei khimii			
Zh(urn), obshch(ei) khimii				
ZhPKh	Zhurnal prikladnoi khimii			
Zh(urn), prikl. khimii				
ZhSKh	Zhurnal strukturnoi khimii			
Zh(urn), strukt. khimii				
ZhTF	Zhurnal tekhnicheskoi fiziki			
Zh(urn), tekhn. fiz.				
Zh(urn), vyssh. nervn. deyat. (im. P. Pavlova)	Zhurnal vysshego nervnogo deyatelnosti (im. I. P. Pavlova)			
			19	1949
			23	1950
			1	1950
			26	1956
			1	1958

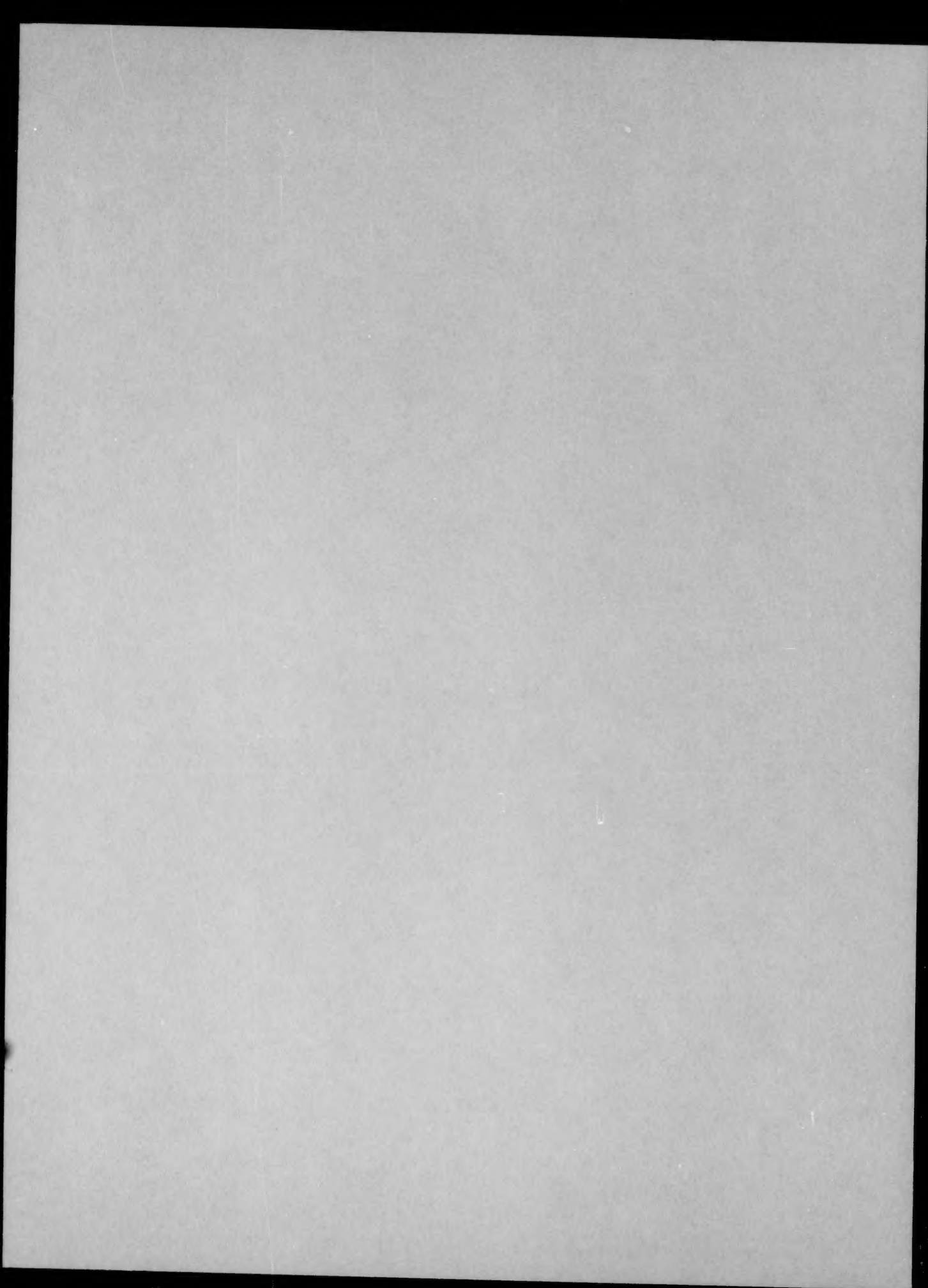


SIGNIFICANCE OF ABBREVIATIONS MOST FREQUENTLY  
ENCOUNTERED IN SOVIET PERIODICALS

FIAN	Phys. Inst. Acad. Sci. USSR
GDI	Water Power Inst.
GITI	State Sci.-Tech. Press
GITTL	State Tech. and Theor. Lit. Press
GONTI	State United Sci.-Tech. Press
Gosenergoizdat	State Power Press
Goskhimizdat	State Chem. Press
GOST	All-Union State Standard
GTTI	State Tech. and Theor. Lit. Press
IL	Foreign Lit. Press
ISN (Izd. Sov. Nauk)	Soviet Science Press
Izd. AN SSSR	Acad. Sci. USSR Press
Izd. MGU	Moscow State Univ. Press
LEIIZhT	Leningrad Power Inst. of Railroad Engineering
LET	Leningrad Elec. Engr. School
LETI	Leningrad Electrotechnical Inst.
LETIIZhT	Leningrad Electrical Engineering Research Inst. of Railroad Engr.
Mashgiz	State Sci.-Tech. Press for Machine Construction Lit.
MEP	Ministry of Electrical Industry
MES	Ministry of Electrical Power Plants
MESEP	Ministry of Electrical Power Plants and the Electrical Industry
MGU	Moscow State Univ.
MKhTI	Moscow Inst. Chem. Tech.
MOPI	Moscow Regional Pedagogical Inst.
MSP	Ministry of Industrial Construction
NII ZVUKSZAPIOI	Scientific Research Inst. of Sound Recording
NIKFI	Sci. Inst. of Modern Motion Picture Photography
ONTI	United Sci.-Tech. Press
OTI	Division of Technical Information
OTN	Div. Tech. Sci.
Stroizdat	Construction Press
TOE	Association of Power Engineers
TsKTI	Central Research Inst. for Boilers and Turbines
TsNIEL	Central Scientific Research Elec. Engr. Lab.
TsNIEL-MES	Central Scientific Research Elec. Engr. Lab.-Ministry of Electric Power Plants
TsVTI	Central Office of Economic Information
UF	Ural Branch
VIESKh	All-Union Inst. of Rural Elec. Power Stations
VNIIM	All-Union Scientific Research Inst. of Metrology
VNIIZhDT	All-Union Scientific Research Inst. of Railroad Engineering
VTI	All-Union Thermotech. Inst.
VZEI	All-Union Power Correspondence Inst.

NOTE: Abbreviations not on this list and not explained in the translation have been transliterated, no further information about their significance being available to us. -Publisher.





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